



HAL
open science

Exploring Cholinergic Compounds for Peripheral Neuropathic Pain Management: A Comprehensive Scoping Review of Rodent Model Studies

Edouard Montigné, David Balayssac

► **To cite this version:**

Edouard Montigné, David Balayssac. Exploring Cholinergic Compounds for Peripheral Neuropathic Pain Management: A Comprehensive Scoping Review of Rodent Model Studies. *Pharmaceuticals*, 2023, 16 (10), pp.1363. 10.3390/ph16101363 . hal-04285363

HAL Id: hal-04285363

<https://hal.science/hal-04285363>

Submitted on 14 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Review

Exploring Cholinergic Compounds for Peripheral Neuropathic Pain Management: A Comprehensive Scoping Review of Rodent Model Studies

Edouard Montigné¹ and David Balayssac^{2,*} 

¹ INSERM, U1107, NEURO-DOL, Université Clermont Auvergne, F-63000 Clermont-Ferrand, France; edouard.montigne@gmail.com

² UMR1107, NEURO-DOL, INSERM, Direction de la Recherche Clinique et de l'Innovation, Université Clermont Auvergne, CHU Clermont-Ferrand, F-63000 Clermont-Ferrand, France

* Correspondence: dbalayssac@chu-clermontferrand.fr

Abstract: Neuropathic pain affects about 7–8% of the population, and its management still poses challenges with unmet needs. Over the past decades, researchers have explored the cholinergic system (muscarinic and nicotinic acetylcholine receptors: mAChR and nAChR) and compounds targeting these receptors as potential analgesics for neuropathic pain management. This scoping review aims to provide an overview of studies on peripheral neuropathic pain (PNP) in rodent models, exploring compounds targeting cholinergic neurotransmission. The inclusion criteria were original articles on PNP in rodent models that explored the use of compounds directly targeting cholinergic neurotransmission and reported results of nociceptive behavioral assays. The literature search was performed in the PubMed and Web of Science databases (1 January 2000–22 April 2023). The selection process yielded 82 publications, encompassing 62 compounds. The most studied compounds were agonists of $\alpha 4\beta 2$ nAChR and $\alpha 7$ nAChR, and antagonists of $\alpha 9/\alpha 10$ nAChR, along with those increasing acetylcholine and targeting mAChRs. Studies mainly reported antinociceptive effects in traumatic PNP models, and to a lesser extent, chemotherapy-induced neuropathy or diabetic models. These preclinical studies underscore the considerable potential of cholinergic compounds in the management of PNP, warranting the initiation of clinical trials.

Keywords: acetylcholine; muscarinic acetylcholine receptor; nicotinic acetylcholine receptor; peripheral neuropathic pain; rodents



Citation: Montigné, E.; Balayssac, D. Exploring Cholinergic Compounds for Peripheral Neuropathic Pain Management: A Comprehensive Scoping Review of Rodent Model Studies. *Pharmaceuticals* **2023**, *16*, 1363. <https://doi.org/10.3390/ph16101363>

Academic Editor: Sergio Marques Borghi

Received: 2 August 2023

Revised: 1 September 2023

Accepted: 14 September 2023

Published: 27 September 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”. In particular, peripheral neuropathic pain (PNP) is defined as “a direct consequence of a lesion or disease of the somatosensory nervous system and may be felt in areas with no tissue damage”, and more precisely, in the peripheral nervous system (PNS) [1]. These injuries of the peripheral somatosensory system result in maladaptive responses that can cause pain that is either spontaneous or evoked by sensory stimuli, as an increased response to a painful stimulus (hyperalgesia), or a painful response to a normally nonpainful stimulus (allodynia) [2].

Many etiologies can explain PNP, among which traumatic causes (e.g., phantom limb pain, postsurgical/traumatic neuropathy), toxic causes (e.g., chemotherapy-induced peripheral neuropathy—CIPN), and metabolic causes (e.g., hyperglycemic conditions) are found [3].

Approximately 7–8% of the general population worldwide experience PNP, with prevalence rates ranging from 0.9% to 17.9% [4]. Guidelines for the first-line pharmacological management of PNP include gabapentin, gabapentin extended release/enacarbil,

pregabalin, serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and tricyclic antidepressants [5]. However, the efficacy of therapeutic strategies remains limited, with several and underassessed safety concerns [6–8], and innovative strategies are particularly needed [9].

The involvement of cholinergic neurotransmission in pain processes has been shown in many studies and could become a new therapeutic target for the management of PNP (for a review, see [10]).

Acetylcholine acts as one of the most prominent neurotransmitters in both the central nervous system (CNS) and PNS, particularly at the ganglionic level of the autonomous nervous system. After its release from cholinergic cells, acetylcholine is quickly metabolized by acetylcholine esterase (AChE) into choline and acetate, and thereafter, biosynthesized to acetylcholine by choline acetyltransferase (ChAT) at the neuronal level. Cholinergic neurotransmission involves two types of receptors: nicotinic acetylcholine receptors (nAChRs), and muscarinic acetylcholine receptors (mAChRs) [11].

The nAChRs are ionotropic receptors consisting of five individual subunits that arrange in a homo- or heteromeric combination and belong to the superfamily of pentameric ligand-gated ion channels (pLGICs), also known in vertebrates as the Cys-loop family. The member subunits of the Cys-loop family contain a disulfide cysteine bridge in the extracellular domain which closes a loop comprising 13 amino acids. Besides the nAChRs, the Cys-loop family includes the serotonin type 3 receptors (5-HT₃), gamma aminobutyric acid type A receptors (GABA_A) and glycine receptors [12]. A total of 19 different nAChR subunits have been identified: α 1– α 10, β 1– β 4, γ , δ , and ϵ subunits [12]. Myriad nAChR subtypes can be formed by different combinations of these subunits. For example, α 4 and β 2 subunits assemble together and comprise the most abundant nAChR subtype, α 4 β 2 [13]. nAChRs regulate the flow of mainly sodium, potassium and calcium ions across the cell membrane [14].

The mAChRs are metabotropic receptors and are represented by five types of receptors, including m1AChR, m2AChR, m3AChR, m4AChR, and m5AChR. mAChRs are separated into two subtypes: excitatory (m1AChR, m3AChR, and m5AChR), and inhibitory (m2AChR and m4AChR). m1AChR, m3AChR, and m5AChR couple to a Gq protein, activating the phospholipase C pathway and increasing the intracellular calcium concentration. The m2AChRs and m4AChRs receptors couple to a Gi/o protein, inhibiting the adenylate cyclase pathway and resulting in a decrease in the amount of intracellular cyclic adenosine monophosphate [11,15].

The implications of the acetylcholine neurotransmission in pain have been demonstrated with a tonic cholinergic inhibition of spinal nociceptive transmission in rats [16], and nerve injury-induced loss of this cholinergic tone underlies the analgesic effects of cholinergic agonists in neuropathic pain [17,18]. Muscarinic signaling is vital in pain modulation, with direct activation of mAChRs reducing pain and mAChRs inhibition inducing nociceptive hypersensitivity [19]. The antinociceptive effects of systemically administered donepezil (AChE inhibitor) are linked to GABAergic signaling downstream of mAChRs, suggesting that cholinergic neurons' inhibitory action may be mediated through GABA release [20]. Intrathecally administered AChE inhibitors, like neostigmine, reduce inflammatory hypersensitivity primarily through m2AChR activation in the spinal cord [21]. The m2AChR and m4AChR receptors predominantly mediate antinociception, while m1AChR and m3AChR have minimal involvement in this process [22].

At the spinal level, presynaptic cholinergic receptors play a significant role in modulating nociceptive transmission, with reports of both excitation and inhibition. Neuronal subpopulations in the dorsal root ganglia (DRG) express α 7 nAChRs and respond to α 7-selective positive allosteric modulators with a calcium rise, but the functional significance remains unclear [23]. mAChRs in the DRG and trigeminal ganglia modulate primary afferent input onto spinal or medullary dorsal horn neurons, leading to inhibition of glutamate release [24,25]. Activation of m2AChR and m4AChR inhibits excitatory synaptic inputs from primary afferents into the spinal cord by targeting voltage-gated calcium channels

in primary sensory neurons [26]. Additionally, the m5AChR subtype has a more complex role, mediating positive effects on primary afferent terminals while potentially increasing glutamate release from spinal interneurons [26].

Supraspinal centers, such as the serotonergic raphe nuclei and adrenergic centers in the locus coeruleus and rostral ventromedial medulla (RVM), play a key role in endogenous nociception control through descending modulation of spinal function. Nicotinic cholinergic signaling in brainstem nuclei stimulates descending inhibitory pathways and mediates antinociceptive effects via interactions with $\alpha 2$ adrenergic, 5-HT_{1c/2}, and 5-HT₃ serotonergic receptors, and m2AChR in the lumbar spinal cord [27]. Studies also show antinociceptive effects from nAChR agonists in the RVM via activation of $\alpha 4\beta 2$ nAChRs (and to a lesser extent, via $\alpha 7$ nAChRs) [28]. Finally, ChAT-Cre mice have demonstrated direct descending control of spinal sensory transmission by brainstem cholinergic neurons [29].

This scoping review aims to provide an overview of studies conducted in rodent PNP models exploring pharmacological compounds that target cholinergic neurotransmission, including the modulation of acetylcholine neurotransmission, nAChRs, and mAChRs.

2. Materials and Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines in the study process [30].

2.1. Eligibility Criteria

The inclusion criteria encompassed original articles on PNP in rodent models (in vivo) that investigated the use of compounds directly targeting cholinergic neurotransmission and reported results of nociceptive behavioral assays.

The exclusion criteria encompassed non-English manuscripts, specific types of manuscripts (reviews, meta-analyses, case reports, books, and conference abstracts), publications lacking available abstracts, in vitro or ex vivo studies, and medicinal chemistry reports. Additionally, publications indirectly exploring cholinergic neurotransmission were excluded from the systematic review. For instance, studies using AChRs antagonists to investigate the involvement of AChRs in the analgesic effect of non-cholinergic compounds were not included.

2.2. Information Sources and Search Strategy

We conducted literature retrieval in the following databases: PubMed (MEDLINE, National Library of Medicine), and Web of Science (Clarivate Analytics PLC). No registers, websites, organizations, reference lists, or other sources were used. The bibliographical search was performed on 22 April 2023, and starting from 1 January 2000.

For PubMed, the sequence of keywords was “(acetylcholine) and ((neuropathy) or (neuropathic pain)) and ((rat) or (mouse)) and ((muscarinic) or (nicotinic))”. For Web of Science, the sequence of keywords was “*acetylcholine (All Fields) AND (neuropathic pain) or (neuropathy) (All Fields) AND (rat) or (mouse) (All Fields) AND (muscarinic) or (nicotinic) (All Fields)*”.

2.3. Study Selection, Data Collection Process and Data Items

All the references from PubMed and Web of Science were extracted and organized using Zotero software (version 6.0.26, Roy Rosenzweig Center for History and New Media) to create a Zotero bibliographic database. This database included the following details for each publication: authors, title, journal, year, abstract, and DOI (Digital Object Identifier). Subsequently, this Zotero bibliographic database was exported to Excel software (version 2021, Microsoft) for analysis.

Initial publication selection, based on title and abstract, was carried out by the authors EM and DB. Following this initial screening, all the authors conducted a second round of selection based on the full-text of the publications and in accordance with the inclusion/exclusion criteria. In cases where discrepancies regarding the inclusion/exclusion

criteria arose for a publication, a consensus among the authors was sought to determine whether to include or exclude the publication.

The researchers extracted the following data from the included manuscripts: title, author, year, DOI, type of PNP, rodent species, sex of animals, name of the compounds, targeted AChRs, behavioral tests and main results.

3. Results

3.1. Study Selection and Characteristics

The process for selection and inclusion of publications is presented in Figure 1. A total of 82 publications were selected and analyzed, and these encompassed 62 cholinergic compounds.

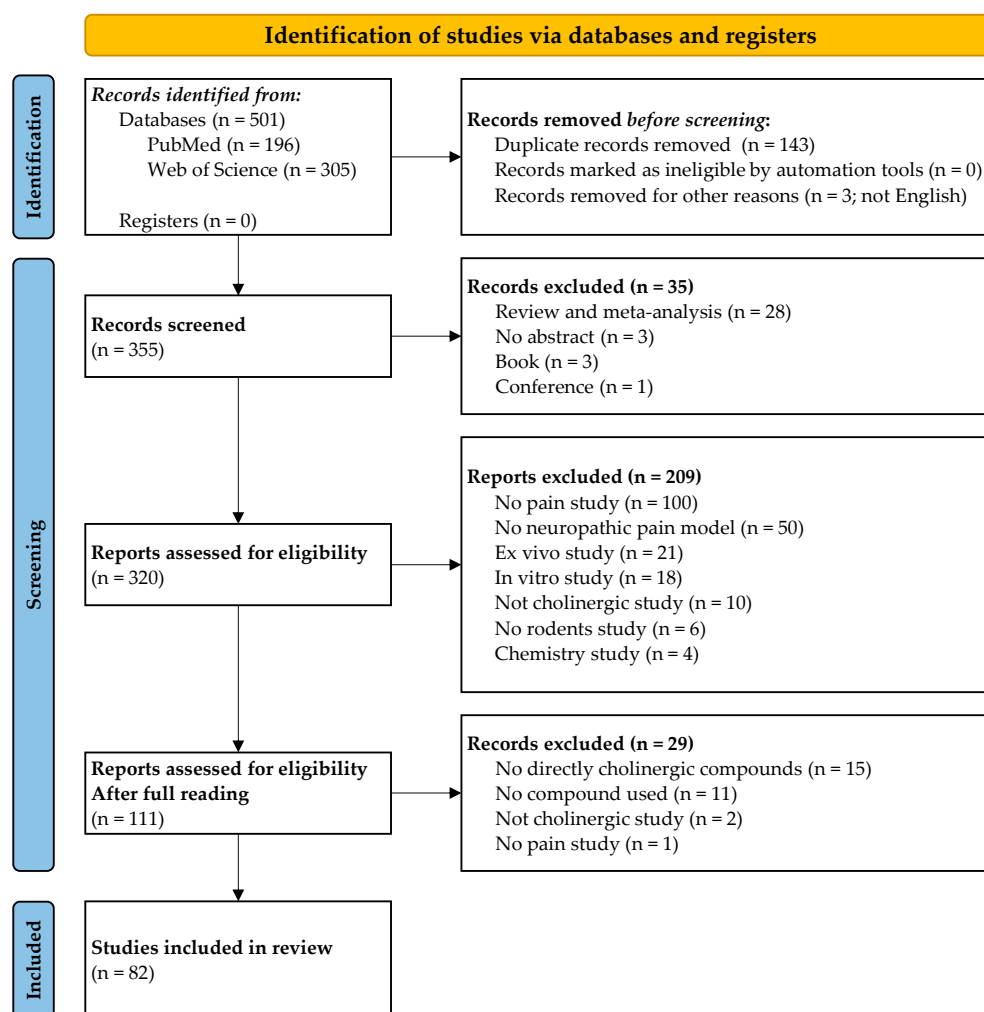


Figure 1. PRISMA flow chart of study selection.

Among the publications selected, 58 used animal models of traumatic PNP, 23 CIPN models and 5 diabetic PNP models (Supplementary Materials, Table S1).

For traumatic PNP, nine different models were used as follows:

- Chronic constriction injury (CCI, $n = 24$);
- Partial sciatic nerve ligation (PSL, $n = 18$);
- Spinal nerve ligation (SNL, $n = 13$);
- Spared nerve injury (SNI, $n = 2$);
- Common peroneal nerve ligation (CPNL, $n = 2$);
- Cuff model (CM, $n = 1$);
- Sciatic nerve crush injury (SCNI, $n = 1$);
- Sciatic nerve transection (SNT, $n = 1$);

- Tibial nerve transection (TNT, $n = 1$).

Among the CIPN models, the oxaliplatin model ($n = 14$) was the most used, but other models such as paclitaxel ($n = 6$), vincristine ($n = 4$), and bortezomib ($n = 1$) were also described. Finally, two models of diabetic PNP were used: streptozotocin-induced peripheral neuropathy (SZT, $n = 4$), and the high-fat diet (HFD, $n = 1$).

3.2. Pharmacological Compounds Increasing the Acetylcholine Neurotransmission

To modulate acetylcholine neurotransmission, seven pharmacological compounds with different mechanisms of actions have been tested, including AChE inhibitors, inhibitors of acetylcholine exocytosis, and acetylcholine precursors (Table 1). All these compounds act to increase the quantity of acetylcholine in the synaptic cleft.

AChE inhibitors were the most commonly investigated compounds, such as ambenonium chloride, donepezil, huperzine-A, neostigmine, and physostigmine. All these compounds have been tested in the three animal models of PNP. Most of the compounds induced antinociceptive effects, both on mechanical and thermal hypersensitivity [20,31–37]. A low dose of neostigmine (intrathecal injection, 0.3 ng) did not produce significant antinociceptive effects [38].

Botulinum neurotoxin type A has been used to inhibit the exocytosis of acetylcholine and has shown a persistent antinociceptive effect on mechanical hypersensitivity [39,40].

Finally, citicoline, a precursor of choline, exhibited antinociceptive properties on mechanical hypersensitivity after intracerebroventricular injection or nerve application [41–43].

3.3. Pharmacological Compounds Targeting Nicotinic Acetylcholine Receptors

3.3.1. Unspecific Targeting of Nicotinic Acetylcholine Receptors

Four compounds unspecifically targeting nAChRs were identified: epibatidine, nicotine, S(–)-nornicotine, and R(+)-nornicotine (Table 2).

Nicotine was the most studied compound at various doses and routes (1–30 nmol i.t., 0.1–2 mg/kg s.c., and 0.3–1.75 mg/kg i.p.), mainly in traumatic PNP models, with one study on a CIPN model (paclitaxel). In several publications, nicotine demonstrated analgesic properties on mechanical and thermal hypersensitivity. It showed a decrease in mechanical allodynia in a time- and dose-dependent manner [18,44–49]. However, chronic administration of nicotine (24 mg/kg/day, osmotic pump) induced a dose-dependent and stable mechanical hypersensitivity [50]. Similarly, repeated administrations of nicotine induced a decrease in its analgesic effects (heat hypersensitivity) [51]. Other studies have also reported a reduction in mechanical and thermal hypersensitivity [52,53]. Two enantiomers, S(–)-nornicotine and R(+)-nornicotine, dose-dependently reversed mechanical hypersensitivity [54].

Finally, epibatidine has also been found to dose-dependently reverse mechanical allodynia in traumatic PNP [18,48,55].

3.3.2. Specific Targeting of $\alpha 4\beta 2$ Nicotinic Acetylcholine Receptors

Ten compounds specifically targeting of $\alpha 4\beta 2$ nAChRs have been identified. Nine of them were agonists ([123/125I]5IA, A-366833, A-85380, NS9283, ABT-418, ABT-594, Bee venom, C-9515, RJR-2403, and TC-2559 [46,55–66]), and one a partial agonist (Sazetidine A [56]) (Table 3). These compounds were primarily tested in traumatic PNP models.

All the tested compounds produced antinociceptive effects, and mostly on mechanical hypersensitivity. However, NS9283 and A-85380 (administered at low pmol dose intrathecally) did not show any effects on mechanical or thermal hypersensitivity in traumatic PNP [48,67].

3.3.3. Specific Targeting of $\alpha 7$ Nicotinic Acetylcholine Receptors

Seventeen compounds targeting $\alpha 7$ nAChRs were identified. Among them, ten were $\alpha 7$ nAChR agonists, two were $\alpha 7$ nAChR silent agonists, three were positives allosteric modulators (PAM) of $\alpha 7$ nAChRs, one was an $\alpha 3\beta 4$ and $\alpha 7$ nAChRs antagonist, and one

was an $\alpha 7$ nAChRs + m4AChRs agonist (Table 4). These compounds were mostly tested in traumatic PNP models.

Among the $\alpha 7$ nAChR agonists, all the tested compounds ((R)-ICH3, choline, cobratoxin, DM489, GAT107, PAM-4, PHA-543613, PNU-28298, PNU-282987, and TC-7020) exhibited antinociceptive effects on mechanical and thermal hypersensitivity [46,68–76]. While GAT107 was effective on mechanical hypersensitivity, no effect was reported on thermal hypersensitivity [72].

The two $\alpha 7$ nAChR silent agonists, NS6740 and R-47, demonstrated antinociceptive effects on mechanical hypersensitivity [77,78].

Regarding the three PAM of $\alpha 7$ nAChRs, only PAM-2 and PNU-120596 had analgesic effects [69,73,79], but NS1738 had no effect on mechanical and thermal hypersensitivity [69].

The $\alpha 3\beta 4$ and $\alpha 7$ nAChRs antagonist, α -conopeptides Eu1.6 [80], and the $\alpha 7$ nAChRs + m4AChRs agonist, DXL-A-24 [81], both decreased mechanical hypersensitivity.

3.3.4. Specific Targeting of $\alpha 9/\alpha 10$ Nicotinic Acetylcholine Receptors

We identified seventeen $\alpha 9/\alpha 10$ nAChR antagonists (Table 5). These compounds have been tested in traumatic and CIPN PNP models, but not in diabetic models.

Most of the studies explored α -conotoxins and derivatives as potent antagonists of $\alpha 9/\alpha 10$ nAChR, including α -conotoxin AuIB, α -conotoxin MII, α -conotoxin Mr1.1 [S4Dap], α -conotoxin RgIA, α -conotoxin RgIA4, α -conotoxin RgIA-5474, [2,8]-alkyne Vc1.1 3, GeXIVA[1,2], GeXIVA[1,4], α -conotoxin Vc1.1, Vc1.1[N9R], and [P6O]Vc1.1. Doses ranged from 0.036 to 60 μg (i.m. route), from 0.128 to 80 $\mu\text{g}/\text{kg}$ (s.c. route), and from 0.02 to 2 nmol (i.t. route).

Nearly all the $\alpha 9/\alpha 10$ nAChR antagonists, including (\pm)-18-MC, (+)-catharanthine, α -conotoxins AuIB, α -conotoxins MII, α -conotoxins Mr1.1 [S4Dap], α -Conotoxin RgIA, α -conotoxins RgIA4, α -Conotoxin RgIA-5474, [2,8]-alkyne Vc1.1 3, α -conotoxins Vc1.1, Vc1.1[N9R], GeXIVA[1,2], GeXIVA[1,4], ZZ-204G, and ZZ1-61c, presented antinociceptive effects on mechanical and thermal hypersensitivity [80,82–104]. [P6O]Vc1.1 had no effect on mechanical hypersensitivity [85], while α -conotoxins RgIA4 (assessed in paclitaxel-related CIPN model) [98], GeXIVA[1,2] (assessed in oxaliplatin-related CIPN model) [102], and ZZ-204G (assessed with the tail flick test in naïve animals) [89], had no effects on thermal hypersensitivity.

3.4. Pharmacological Compounds Targeting Muscarinic Acetylcholine Receptors

Eight compounds targeting mAChRs have been identified, including one mAChR non-selective agonist (oxotremorine), one mAChR antagonist (scopolamine), one agonist of m2/m4AChRs and antagonist of m1/m3/m5AChRs (PTAC), one m4/ $\alpha 7$ AChRs agonist (DXL-A-24), one m1/m4AChRs agonist (McNA-343), one m1AChR agonist (PPBI), and two m1AChR antagonists (pirenzepine and VU0255035) (Table 6). These compounds were mostly tested in traumatic PNP models.

All these compounds induced antinociceptive effects in PNP models and mostly on mechanical hypersensitivity [38,81,105–110]. Only McNA-343 (m1/m4AChRs agonist) did not alleviate thermal hypersensitivity [38]. Scopolamine (mAChRs antagonist) injected in the anterior cingulate cortex decreased the autotomy behavior of animals (sciatic nerve section) [107].

Surprisingly, both agonist (PPBI) and antagonists (pirenzepine and VU0255035) of m1AChRs demonstrated antinociceptive effects in PNP models [109,110].

Table 1. Description of studies assessing pharmacological compounds modulating the acetylcholine neurotransmission.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
Ambenonium chloride	AChE inhibitors	0.05 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs Conditioned place preference	\searrow M 0 spontaneous pain	[34]
		0.3–1 mg/kg, i.p.	Traumatic	Rat (σ)	Paw pressure	\searrow M	[20]
0.3–1.0 mg/kg, i.p.		Traumatic	Rat (σ)	Paw pressure	Dose-dependent \searrow M (0.6 and 1 mg/kg)	[31]	
5–10 mg/kg, p.o.		CIPN + traumatic	Rat (σ)	Electronic Von Frey Paw immersion 10 °C and 46 °C	\searrow M + T	[32]	
5 mg/kg, p.o.		CIPN	Rat (σ)	Electronic Von Frey Tail immersion 10 °C	\searrow M + T	[33]	
Huperzine-A		0.1–0.15 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs Conditioned place preference	\searrow M 0 spontaneous pain	[34]
Neostigmine		2 mg, i.t.	Traumatic	Rat (σ)	Von Frey hairs	\searrow M	[36]
		0.3–3 ng, i.t.	Traumatic	Mouse (σ)	Plantar test Von Frey hairs	Dose-dependant \searrow M + T (3 ng)	[38]
Physostigmine		0.1–0.5 μ g, i.t.	Diabetic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (0.5 μ g)	[37]
		15 nmol, i.t.	Traumatic	Mouse (σ)	Von Frey hairs	\searrow M	[35]
BoNT/A	Acetylcholine exocytosis inhibitors	15 pg, i.p.	Traumatic	Mouse (σ)	Electronic Von Frey	\searrow M	[39]
BoNT/A Dysport® BoNT/A Botox®		20 U/kg, s.p.	CIPN	Rat (σ)	Paw pressure	\searrow M	[40]
Citicoline		Acetylcholine precursor	0.4–0.8 mL (100 μ mol/L), p.n.	Traumatic	Rat (σ)	Von Frey hairs	\searrow M
	0.5–2 μ mol, i.c.v.		Traumatic	Rat (σ)	Paw pressure	Dose- and time-dependent \searrow M (1 and 2 μ mol)	[42]
	0.5–2 μ mol, i.c.v.		CIPN	Rat (σ)	Paw pressure	Dose- and time-dependent \searrow M (1 and 2 μ mol)	[43]

BoNT/A: botulinum neurotoxin type A; AChE: acetylcholine esterase; p.o.: per os; i.p.: intraperitoneal; i.t.: intratechal; p.n.: perinervous; s.p.: subplantar; i.c.v.: intracerebroventricular; \searrow : decrease; 0: no effect; M: mechanical sensitivity; T: thermal sensitivity; σ : male.

Table 2. Description of studies assessing pharmacological compounds targeting nicotinic acetylcholine receptors.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
Epibatidine	nAChRs agonists	0.03–0.3 nmol, i.t.	Traumatic	Mouse (σ)	Electronic Von Frey Plantar test	Dose-dependent \searrow M (all doses effective)	[18]

Table 2. Cont.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.		
Epibatidine		0.3–10.0 µg/kg, s.c.	Traumatic	Rat (♂)	Paw pressure	Dose-dependent ↓ M (all doses effective)	[55]		
		0.036–0.36 pmol, i.t.	Traumatic	Rat (♂)	Paw pressure	Dose-dependent ↓ M	[48]		
		0.1–1.5 mg/kg, s.c.	Traumatic	Mouse (♂)	Von Frey hairs	Dose- and time-dependent ↓ M (1 and 1.5 mg/kg)	[45]		
		0.1–10 nmol, i.t.	Traumatic	Rat (♂)	Electronic Von Frey	Dose- and time-dependent ↓ M (1 nmol)	[46]		
		3–30 nmol, i.t.	Traumatic	Mouse (♂)	Electronic Von Frey Plantar test	Dose-dependent ↓ M (10 and 30 nmol)	[18]		
		2.2–6.5 nmol, i.t.	Traumatic	Rat (♂)	Paw pressure	Dose-dependent ↓ M	[48]		
		0.25–1.75 mg/kg, i.p.	Traumatic	Mouse (♂ + ♀)	Von Frey hairs	Dose-dependent ↓ M	[49]		
		0.25–25 µg, i.c.v.	Traumatic	Mouse (♂ + ♀)	Von Frey hairs	Dose-dependent ↓ M	[49]		
Nicotine	nAChRs agonists	0.25–17.5 µg, i.t.	Traumatic	Mouse (♂ + ♀)	Von Frey hairs	Dose-dependent ↓ M	[49]		
		25–100 µg, i.pl.	Traumatic	Mouse (♂ + ♀)	Von Frey hairs	Dose-dependent ↓ M	[49]		
		4 or 10 mg/kg/day, s.c.	Traumatic	Rat (♂)	Paw pressure	↗ M	[50]		
		20 nmol/day/4 days, p.n. 1–20 nmol, p.n.	Traumatic	Mouse (♂)	Von Frey hairs Plantar test	↓ M (preventive effect) Dose-dependent ↓ M + T (5 and 20 nmol)	[47]		
		2 mg/kg, s.c.	Traumatic	Mouse (♂)	Von Frey hair	↓ T	[51]		
		1 mg/kg, i.v.	Traumatic	Mouse (♂)	Von Frey hairs Plantar test Tail-flick	↓ M + T	[52]		
		20 nmol, p.n.	Traumatic	Mouse (♂)	Von Frey hair Plantar test	↓ M + T	[53]		
		0.3–0.9 mg/kg, i.p. 24 mg/kg/day, s.c.	CIPN	Mouse (♂)	Von Frey hairs	Dose-dependent ↓ M (0.6 and 0.9 mg/kg) ↓ M (preventive effect)	[44]		
		S(-)-nornicotine		5–20 mg/kg, i.p.	Traumatic	Rat (♂)	Paw pressure	Dose-dependent ↓ M (20 mg/kg)	[54]
		R(+)-nornicotine		10–15 mg/kg, i.p.	Traumatic	Rat (♂)	Paw pressure	Dose-dependent ↓ M (15 mg/kg)	[54]

i.p.: intraperitoneal; i.t.: intratechal; s.c.: subcutaneous; i.c.v.: intracerebroventricular; i.pl.: intraplantar; p.n.: perinervous; ↓: decrease; ↗: increase; M: mechanical sensitivity; T: thermal sensitivity; ♀: female; ♂: male.

Table 3. Description of studies assessing pharmacological compounds targeting $\alpha 4\beta 2$ nicotinic acetylcholine receptors.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
[123/125I]5IA	$\alpha 4\beta 2$ nAChR agonists	1–100 nmol, i.c.v.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (50 and 100 nmol)	[57]
		1–10 nmol, i.c.v.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (3 and 10 nmol)	[63]
A-366833		1.9–19 μ mol/kg, i.p.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (all doses effective)	[64]
		1–6 mg/kg, i.p.	Traumatic + Diabetic +CIPN	Rat (σ)	Paw pressure	\searrow M	[65]
A-85380		0.125–1 μ mol/kg, i.p.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (0.75 and 1 μ mol/kg)	[66]
		<pmol, i.t.	Traumatic	Rat (σ)	Paw pressure	0 M	[48]
NS9283		35 mmol/kg, i.p.	Traumatic	Rat (σ)	Von Frey hair	0 M	[67]
ABT-418		1–20 nmol, p.n.	Traumatic	Mouse (σ)	Von Frey hairs Plantar test	\searrow M + T	[53]
ABT-594		3–100 μ g/kg, s.c.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (10–100 μ g/kg)	[55]
		0.01–0.3 μ mol/kg, i.p.	CIPN	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (0.1–0.3 μ mol/kg)	[59]
Bee venom		0.25 mg/kg, s.c.	CIPN	Rat (σ)	Tail immersion test	\searrow T	[61]
C-9515		0.001–0.01 mg/kg, i.p.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (0.003 and 0.01 mg/kg)	[58]
RJR-2403		1–100 nmol, i.t.	Traumatic	Rat (σ)	Electronic Von Frey	\searrow M	[46]
TC-2559		2.28–22.8 μ mol/kg, s.c. 20 nmol, p.n.	Traumatic	Mouse (σ)	Von Frey hairs	Dose-dependent \searrow M (22.8 μ mol/kg) \searrow M	[56]
	1–20 nmol, p.n.	Traumatic	Mouse (σ)	Von Frey hairs Plantar test	\searrow M + T	[53]	
	0.3–3 mg/kg, i.p.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (1 and 3 mg/kg)	[62]	
	20 nmol, p.n. 10 mg/kg, s.c.	Diabetic	Mouse (σ)	Von Frey hair	\searrow M	[60]	

Table 3. Cont.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
Sazetidine A	$\alpha 4\beta 2$ nAChR partial agonist	0.2–20 nmol, p.n.	Traumatic	Mouse (σ)	Von Frey hairs	Dose-dependent \searrow M (20 nmol)	[56]

i.p.: intraperitoneal; i.t.: intratechal; s.c.: subcutaneous; i.c.v.: intracerebroventricular; p.n.: perinervous; s.c.: subcutaneous; \searrow : decrease; 0: no effect; M: mechanical hypersensitivity; T: thermal hypersensitivity; φ : female; σ : male.

Table 4. Description of studies assessing pharmacological compounds targeting $\alpha 7$ nicotinic acetylcholine receptor.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.	
(R)-ICH3	$\alpha 7$ nAChR agonist	30 mg/kg, p.o.	CIPN	Rat (σ)	Paw pressure Von Frey hairs Cold plate (4 °C)	\searrow M + T	[70]	
Choline		100 nmol, i.t.	Traumatic	Rat (σ)	Electronic Von Frey	\searrow M	[46]	
Cobratoxin		0.56–4.5 μ g/kg, i.t.	Traumatic	Rat (σ)	Paw pressure Tail-flick	Dose-dependent \searrow M + T (1.12 and 4.5 μ g/kg)	[68]	
DM489		3–10 mg/kg, p.o.	Diabetic CIPN	Mouse (σ) Mouse (σ)	Cold plate 4 °C Cold plate 4 °C	\searrow T \searrow T	Dose- and time-dependent \searrow M (3 and 10 mg/kg) \searrow T	[73]
		10–30 mg/kg, p.o.						[73]
GAT107		1–10 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hair Plantar test	Dose- and time-dependent \searrow M (3 and 10 mg/kg) \searrow T	[72]	
PAM-4		1–2 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs	Dose- and time-dependent \searrow M (2 mg/kg)	[74]	
PHA-543613		12 μ g, i.t.	Traumatic	Rat (σ)	Electronic von frey Plantar test	\searrow M + T	[71]	
		1–6 mg/kg, s.c.	Traumatic	Mouse (σ)	Von Frey hairs	Dose-dependent \searrow M (6 mg/kg)	[69]	
PNU-28298		1–30 mg/kg, p.o.	Traumatic	Rat (σ)	Paw pressure	Dose-dependent \searrow M	[75]	
PNU-282987		30 mg/kg, p.o.	CIPN	Rat (σ)	Paw pressure	\searrow M	[70]	
		1 μ g/kg, i.t.	Traumatic	Rat (σ)	Paw pressure Tail-flick	\searrow M + T	[68]	
TC-7020		1–10 mg/kg/day, s.c.	Traumatic	Rat (σ)	Von Frey hairs	\searrow M	[76]	

Table 4. Cont.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
NS6740	$\alpha 7$ nAChR silent agonist	1–9 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs	Dose-dependent \searrow M (9 mg/kg)	[77]
R-47		0–10 mg/kg, p.o.	CIPN	Mouse (σ)	Von Frey hairs	Dose- and time-dependent \searrow M (5 and 10 mg/kg)	[78]
PAM-2	$\alpha 7$ nAChR PAM	3 mg/kg, p.o.	Diabetic + CIPN	Mouse (σ)	Cold plate 4 °C	\searrow T	[73]
		2–8 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs	Dose-dependent \searrow M (6 and 8 mg/kg)	[79]
NS1738		30 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs Plantar test	0 M + T	[69]
PNU-120596		1–8 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs Plantar test	\searrow M + T	[69]
α -conopeptides Eu1.6		$\alpha 3\beta 4/\alpha 7$ nAChR antagonist	0.5–24.9 μ g/kg, i.m.	Traumatic	Rat (σ)	Paw pressure	\searrow M
DXL-A-24	$\alpha 7$ nAChR/ m4AChR agonist	0.25–1 mg/kg, p.o. daily	Traumatic	Rat (σ)	Von Frey hairs Hot plate 50 °C	Dose- and time-dependent \searrow M + T (0.5 and 1 mg/kg)	[81]

PAM: positive allosteric modulator; p.o.: per os; i.p.: intraperitoneal; i.m.: intramuscular; i.t.: intratechal; s.c.: subcutaneous; \searrow : decrease; 0: no effect; M: mechanical sensitivity; T: thermal sensitivity; σ : male.

Table 5. Description of studies assessing pharmacological compounds targeting $\alpha 9/\alpha 10$ nicotinic acetylcholine receptors.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
(\pm)-18-MC	$\alpha 9/\alpha 10$ nAChR antagonist	72 mg/kg, p.o.	CIPN	Mouse (σ)	Cold plate 4 °C	\searrow T	[90]
(+)-catharanthine		36–72 mg/kg, p.o.	CIPN	Mouse (σ)	Cold plate 4 °C	\searrow T	[90]
α -conotoxin AulB		0.02–2 nmol, i.t.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (2 nmol)	[82]
		0.36–36 μ g, i.m.	Traumatic	Rat (σ)	Von Frey hairs	\searrow M	[83]
α -conotoxin MII		0.02–2 nmol, i.t.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (2 nmol)	[82]
	0.36–36 μ g, i.m.	Traumatic	Rat (σ)	Von Frey hairs	\searrow M	[83]	
α -conotoxin Mr1.1 [S4Dap]		0.5–25 μ g/kg, nr	Traumatic	Rat (σ)	Electronic Von Frey	Dose-dependent \searrow M (25 μ g/kg)	[91]

Table 5. Cont.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
α -conotoxin RgIA		2–10 nmol, i.m.	Traumatic	Rat (σ)	Paw pressure Electronic Von Frey	\searrow M	[84]
		0.02–0.2 nmol, i.m.	Traumatic	Rat (σ)	Paw pressure	Dose-dependent \searrow M (0.2 nmol)	[92]
		100 mg/kg, i.m.	CIPN	Mouse (σ)	Hot plate 47 °C Electronic Von Frey	\searrow T + M	[93]
		2–10 nmol, i.m.	CIPN	Rat (σ)	Acetone test Cold plate 4 °C	\searrow T	[94]
α -conotoxin RgIA4		0.128–80 μ g/kg, s.c.	CIPN	Mouse + Rat (σ)	Paw pressure Cold plate 4 °C	Dose-dependent \searrow M + T (all doses effective)	[95]
		40 μ g/kg, s.c.	CIPN	Mouse (nr)	Cold plate (decrease of 10 °C/min)	\searrow T	[96]
		40 μ g/kg, s.c.	CIPN	Mouse (nr)	Cold plate (decrease of 10 °C/min)	\searrow T	[97]
	α 9/ α 10 nAChR antagonist	16–80 μ g/kg, s.c.	CIPN	Rat (σ)	Von Frey hairs Cold plate 5 °C Plantar test	Time-dependent \searrow M 0 T	[98]
α -conotoxin RgIA-5474		4–40 μ g/kg, s.c.	CIPN	Mouse (nr)	Cold plate (decrease of 10 °C/min)	\searrow T	[99]
		0.02–2 nmol, i.t.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (2 nmol)	[82]
α -conotoxin Vc1.1		0.36–36 μ g, i.m.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (all doses effective)	[83]
		0.36–3.6 μ g, i.m.	Traumatic	Rat (σ)	Paw pressure	Dose-dependent \searrow M (3.6 μ g)	[101]
		0.036–0.36 μ g, i.m.	Traumatic	Rat (σ)	Paw pressure	Dose-dependent \searrow M	[92]
		60 μ g, i.m.	Traumatic	Rat (σ)	Von Frey hairs	\searrow M	[85]
		27.2–54.2 μ g/kg, i.m.	Traumatic	Rat (σ)	Paw pressure	\searrow M	[80]
[2,8]-alkyne Vc1.1 3		0.03–0.1 mg/kg, i.m.	Traumatic	Rat (σ)	Von Frey hairs	Dose-dependent \searrow M (0.1 mg/kg)	[100]
Vc1.1[N9R]		0.3–15 nmol/kg, i.m.	Traumatic	Rat (σ)	Paw pressure	\searrow M	[86]
[P6O]Vc.1.1		60 μ g, i.m.	Traumatic	Rat (σ)	Von Frey hairs	0 M	[85]

Table 5. Cont.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
GeXIVA[1,2]	$\alpha 9/\alpha 10$ nAChR antagonist	0.5–2 nmol, i.m.	Traumatic	Rat (σ)	Electronic Von Frey	Dose-dependent \searrow M (All doses effective)	[104]
		0.3–1.2 nmol, i.m.	Traumatic	Rat (σ)	Electronic Von Frey Von Frey hairs	\searrow M	[87]
		32–128 nmol/kg, i.m.	CIPN	Rat (σ)	Von Frey hairs + acetone test + tail-flick	Dose-dependent \searrow (128 nmol/kg) 0 T	[102]
		0.45 mg/kg, i.m.	CIPN	Rat (σ)	Von Frey hairs Tail-flick	\searrow M + T	[103]
GeXIVA[1,4]	$\alpha 9/\alpha 10$ nAChR antagonist	0.5–2 nmol, i.m.	Traumatic	Rat (σ)	Electronic Von Frey	Dose-dependent \searrow M (1 and 2 nmol)	[104]
Oligoarginine R8		20 mg/kg, i.m.	CIPN	Mouse (σ)	Hot plate 47 °C Electronic Von Frey Acetone test	\searrow M + T	[93]
ZZ-204G	$\alpha 9/\alpha 10$ nAChR antagonist	3.6–3600 μ g/kg, i.p.	Traumatic	Rat (σ)	Paw pressure Tail-flick	Dose-dependent \searrow M (360 and 3600 μ g/kg) 0 T	[89]
ZZ1-61c		100 μ g/kg/day, i.p.	CIPN	Rat (σ)	Paw pressure	\searrow M	[88]

p.o.: per os; i.p.: intraperitoneal; i.m.: intramuscular; i.t.: intratechal; s.c.: subcutaneous; nr: not reported; \searrow : decrease; 0: no effect; M: mechanical hypersensitivity; T: thermal hypersensitivity; ♀: female; ♂: male.

Table 6. Description of studies assessing pharmacological compounds targeting muscarinic acetylcholine receptors.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
Oxotremorine	mAChRs non-selective agonist	5–10 μ g, i.t.	Traumatic	Rat (σ)	Von Frey hairs Ethyl chloride spray Plantar test	\searrow M + T	[105]
PTAC	m2-4 AChRs agonist m1-3-5 AChRs antagonist	0.05–0.1 mg/kg, i.p.	Traumatic	Mouse (σ)	Von Frey hairs	\searrow M	[106]

Table 6. Cont.

Compounds	Targets	Doses, Routes	Models	Species (Sex)	Behavioral Assays	Effects	Ref.
Scopolamine	mAChRs antagonist	0.4 µg/µL, ACC	Traumatic	Rat (♂)	Daily autotomy scores	↘ autotomy	[107]
DXL-A-24	m4AChR + α7 nAChR agonist	0.25–1 mg/kg, p.o.	Traumatic	Rat (♂)	Von Frey hairs	Dose-dependent ↘ M (0.5 and 1 mg/kg)	[81]
McNA-343	m1/m4AChRs agonist	18.9–1890 pmol, ACC	Traumatic	Rat (♂)	Electronic Von Frey	Dose-dependent ↘ M (189 and 1890 pmol)	[108]
		3–10 µg, i.t.	Traumatic	Mouse (♂)	Plantar test Von Frey hairs Paw pressure	↘ M 0 T	[38]
PPBI	m1AChR agonist	0.2–100 mmol/kg, p.o.	Traumatic + CIPN	Mouse + Rat (♂)	Tail immersion 13 °C Acetone test Plantar test	Dose-dependent ↘ M + T	[109]
Pirenzepine	m1AChR antagonist	10 mg/kg/d, s.c.	Diabetic + CIPN	Mouse + Rat (♂ + ♀)	Von Frey hairs	↘ M	[110]
VU0255035		10 mg/kg, i.p.	Diabetic	Mouse + Rat (♂ + ♀)	Von Frey hairs	↘ M	[110]

i.p.: intraperitoneal; i.t.: intratechal; s.c.: subcutaneous; p.o.: per os; ACC: anterior cingulate cortex injection; ↘: decrease; 0: no effect; M: mechanical sensitivity; T: thermal sensitivity; ♀: female; ♂: male.

4. Discussion

This review aimed to assess the state of the art regarding compounds targeting acetylcholine neurotransmission for the management of PNP in rodent models.

Among the 82 selected publications, 62 cholinergic compounds were assessed in rodent models of PNP. Almost all the compounds had antinociceptive effects in the PNP models, demonstrating the interest in targeting acetylcholine neurotransmission for pain management. Most of the studies assessed the compounds using traumatic models of PNP, and to a lesser extent, in CIPN or diabetic models. Two third of the studies were conducted with rats, and one third with mice. Most of the studies utilized male animals, and only two studies employed both male and female animals. However, sex differences exist in the context of PNP, particularly concerning the sexually dimorphic nature of neuroimmune pathophysiology [111], which highlights the importance of including subjects of both sexes in preclinical pain research [112].

In two-thirds of the assays, compounds were administered via systemic routes, with the i.p. route accounting for 23.2%, the i.m. route for 18.8%, the s.c. route for 13.6%, and the p.o. route for 11.6%. The remaining third of the assays employed local routes of administration, with the most representative ones being the i.t. route for 18.8%, p.n. for 5.4%, and the i.c.v. route for 4.5%. In spite of the interesting use of local administrations for defining precise mechanisms of action, systemic routes should be encouraged to improve the translationality of the results and drugability of the compounds. The assessment of the analgesic effects of compounds was primarily conducted using tests exploring mechanical hypersensitivity, which accounted for approximately 75% of the tests. Thermal hypersensitivity was less explored, comprising approximately 25% of the tests. Interestingly, in some cases, the same compound demonstrated effectiveness on mechanical hypersensitivity but not on thermal hypersensitivity (e.g., the $\alpha 7$ nAChR agonist GAT107 [72]; the $\alpha 9/\alpha 10$ nAChR antagonists α -conotoxin RgIA4 [98], GeXIVA[1,2] [82], and ZZ-204G [89]; and the m1/m4AChRs agonist McNA-343 [38]). Therefore, the exploration of the analgesic activity of these compounds should be encouraged on both modalities (mechanical and thermal) to better define their effects.

The present review highlights that research has primarily focused on nAChRs compared with mAChRs (Figure 2). Among the nAChRs, the $\alpha 4\beta 2$ nAChR and $\alpha 7$ nAChR agonists, and $\alpha 9/\alpha 10$ nAChR antagonists were the main compounds explored. The first approach was driven by a global activation of nAChRs, thanks to nicotine [44–53]. Epibatidine, a toxic alkaloid isolated and identified from *Epipledobates tricolor* skin (for a review see [113]), was also used in a similar approach [18,48,55], and even though this compound is recognized today as an $\alpha 4\beta 2$ nAChR agonist, it is also able to target $\alpha 7$ nAChR and $\alpha 3\beta 4$ nAChR [113]. A more specific targeting of nAChRs has been tested with specific agonists of $\alpha 4\beta 2$ nAChR and $\alpha 7$ nAChR, and antagonists of $\alpha 9/\alpha 10$ nAChR. The latter were mainly focused on α -conotoxins and derivatives originating from venomous marine cone snails (*Conus species*) [114].

$\alpha 4\beta 2$ nAChR stands out as the most prevalent heteromeric subtype within the brain. Typically labeled as $\alpha 4\beta 2^*$ nAChR, the asterisk acknowledges the potential involvement of additional subunits. When presented in isolation, the $\alpha 4$ and $\beta 2$ subunits coalesce to form two distinctive functional isoforms: the low-sensitivity ($\alpha 4$)₃($\beta 2$)₂ and high-sensitivity ($\alpha 4$)₂($\beta 2$)₃ nAChRs. Notably, the lower acetylcholine sensitivity of ($\alpha 4$)₃($\beta 2$)₂ nAChR constitutes the majority within the cortex [115]. This $\alpha 4\beta 2^*$ nAChR variant assumes a crucial role in nicotine dependence and represents a pharmacological target for smoking cessation aids like varenicline [115].

In contrast, the homopentameric $\alpha 7$ nAChR lacks the synaptic functional adaptations observed in muscle-type and ganglionic nAChRs. The absence of non-alpha subunits influences the agonist binding site, shifting high-affinity agonist binding toward desensitized states and enhancing sensitivity to the widely available acetylcholine precursor, choline [116]. Unique cellular and subcellular distribution patterns for $\alpha 7$ nAChR indicate its distinct roles. These distinctive patterns encompass widespread expression in

non-neuronal cells, including those within the immune system. Notably, $\alpha 7$ nAChR plays a distinctive role in regulating the cholinergic anti-inflammatory pathway. An intriguing attribute of open $\alpha 7$ nAChR is its heightened calcium permeability [116]. Although this characteristic could potentially lead to excitotoxicity akin to NMDA-type glutamate receptors, the normally low open probability of the $\alpha 7$ nAChR receptor channel offsets this risk [114]. It is noteworthy that modifications in intracellular calcium concentration following $\alpha 7$ nAChR stimulation predominantly arise from the release of calcium stored intracellularly rather than calcium influx through $\alpha 7$ nAChR channels, implying a metabotropic-like effect [116].

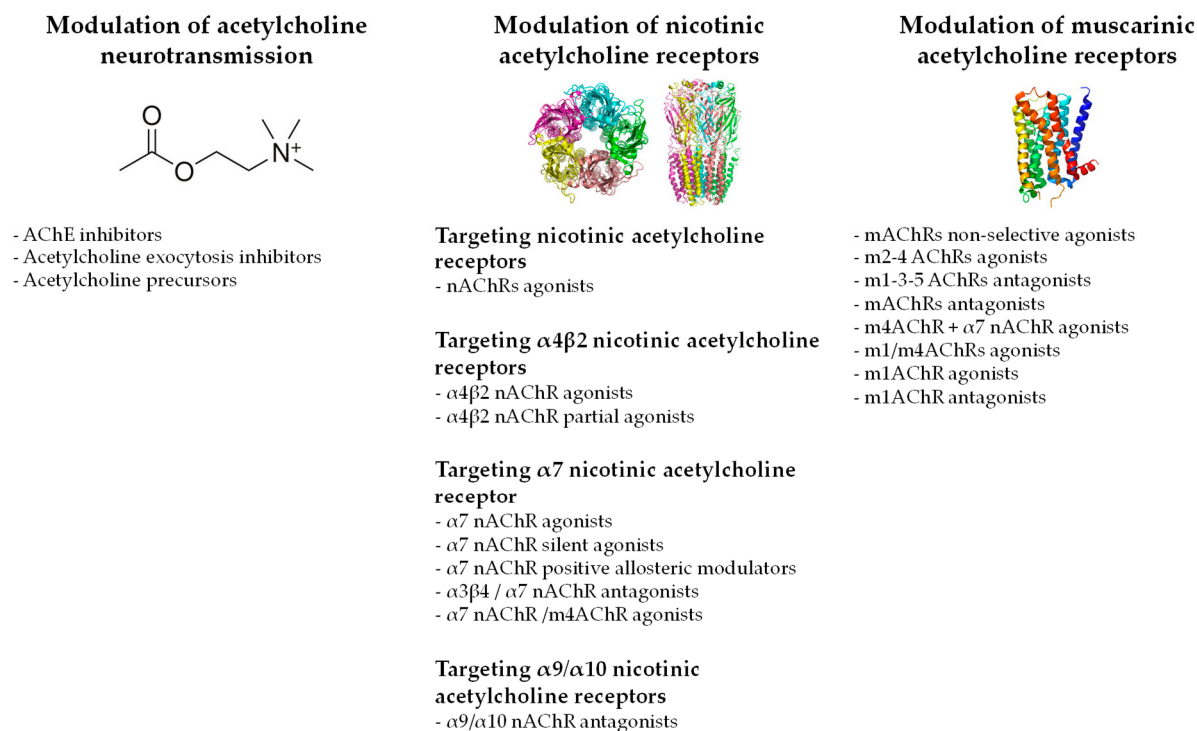


Figure 2. Pharmacological targets identified in the selected publications (image: Wikipedia).

$\alpha 9 / \alpha 10$ nAChR represents a more recently studied subtype. Its primary functions have been elucidated in inner ear mechanosensory hair cells. Considered a non-neuronal nAChR, the $\alpha 9 / \alpha 10$ subtype demonstrates negligible expression of $\alpha 9$ and very low expression of $\alpha 10$ subunits in murine DRG [12,117]. However, in human DRG, around 25% of sensory neurons have been found to express $\alpha 9$ and $\alpha 10$ mRNA [117]. Notably, the $\alpha 9 / \alpha 10$ nAChR holds potential as an intriguing target for inner ear disorders from a pharmacotherapeutic perspective [12]. Beyond auditory disorders, blocking $\alpha 9 / \alpha 10$ nAChRs has displayed analgesic effects linked to the modulation of immune cells and inflammatory processes [13].

Excluding $\alpha 9 / \alpha 10$ nAChR, nAChRs are distributed across neurons in peripheral nociceptive nerve fibers, DRG, the dorsal horn of the spinal cord, the RVM in the brainstem, and the periaqueductal gray, all of which play pivotal roles in pain perception and processing [118]. Moreover, $\alpha 4\beta 2$ nAChRs have been identified within astrocytes in the spinal cord and regions of the brain associated with pain processing [119]. $\alpha 7$ nAChRs display expression in immune and non-immune cells responsible for cytokine production, exercising control over immune cell functions, suppressing the production of pro-inflammatory cytokines, and mitigating inflammatory processes [116].

Finally, the targeting of mAChRs was clearly less explored, with few compounds and a widespread targeting of both agonists and antagonists for specific and unspecific mAChRs (Figure 2). No specific mAChRs emerged as clear pharmacological targets. Moreover, the definition of the compounds' activities can be obscure. For example, both agonists and antagonists of the same m1AChRs induced antinociceptive effects [109,110], which

raises doubt about the selectivity of these compounds. This targeting of mAChRs for pain management remains clearly underexplored, and more research is needed.

Another interesting point is that compounds modulating the acetylcholine neurotransmission (e.g., AChE inhibitors, acetylcholine exocytosis inhibitors, and acetylcholine precursors), which ultimately increase the quantity of acetylcholine in the synaptic cleft, demonstrated analgesic effects (Figure 2) [20,31–37,39–43]. This unspecific strategy stands in stark contrast to the targeting of specific AChRs for pain modulation described in this review. By increasing the quantity of acetylcholine, these compounds promote global activation of nAChRs and mAChRs, which can be opposite to the sought effect in the case of $\alpha 9/\alpha 10$ nAChRs, where an inhibition of the latter is needed for an analgesic effect [120].

Studies on nicotine have explored the desensitization of its activity after chronic exposure, showing a decrease in its antinociceptive effects and even nociceptive sensitization, mediated by a desensitization of $\alpha 4\beta 2$ nAChRs [50]. This desensitization was related to an increase in the phosphorylation of cAMP response element-binding protein (pCREB) in the spinal cord, which is highly correlated with the degree of mechanical hypersensitivity [50]. It is well demonstrated that tobacco smoking has acute antinociceptive effects [121] and chronic pronociceptive ones [122]. Tobacco smoking is a risk factor for chronic pain [122]. This desensitization of nAChRs has also been reported for $\alpha 7$ nAChR and $\alpha 3\beta 4$ nAChR, driving the research from agonists of specific nAChRs to positive allosteric modulators of these nAChRs. Positive allosteric modulators can increase the binding affinity and/or efficacy of an orthosteric agonist (endogenous or exogenous) [123].

To our knowledge, besides BoNT/A, which is mainly authorized for various spasticity disorders, no cholinergic compound is currently authorized for the clinical management of PNP. The use of cholinergic compounds in patients experiencing pain could raise safety concerns regarding the cholinergic mechanism of action. We can extrapolate adverse effects of these compounds from those of AChE inhibitors used in Alzheimer's disease treatment and medications used for smoking cessation (nicotine replacement therapy and varenicline). The most frequently reported adverse events of AChE inhibitors are gastrointestinal issues, including nausea, vomiting, diarrhea, and anorexia [124]. In the case of nicotine replacement therapy, the most commonly reported adverse events include headache, dizziness/light-headedness, nausea/vomiting, gastrointestinal symptoms, sleep/dream problems, and cardiovascular effects (palpitations, chest pain) [125]. With varenicline, the most frequently reported adverse events are nausea, insomnia, abnormal dreams, and headache [126].

Limitations of This Review

The aim of this review was to present an overview of the current studies focused on compounds that modulate cholinergic neurotransmission in the management of PNP in rodent models. This aim was not to report effective compounds on PNP. However, we believe that there is still a publication bias related to the fact that many negative results have not been published [127], and consequently, several studies focused on compounds that modulate cholinergic neurotransmission would be underreported.

5. Conclusions

The objective of this scoping review was to identify the primary targets and compounds studied in animal models of PNP. Besides mAChRs, nAChRs remain the most extensively investigated targets, with specific compounds such as $\alpha 4\beta 2$ nAChR and $\alpha 7$ nAChR agonists, as well as $\alpha 9/\alpha 10$ nAChR antagonists. Notably, for the latter group, a majority of studies have focused on conotoxins and derivatives, representing innovative compounds. In contrast, when it comes to mAChRs, no distinct cholinergic target can be definitively defined based on this review.

The next steps involve a clear delineation of the antinociceptive mechanisms of action, including a more precise identification of the targeted AChRs and the cellular pathways

involved, which, for many of these cholinergic targets, appear to encompass both neuronal and non-neuronal elements, including the immune system.

Overall, these preclinical studies underscore the considerable potential of cholinergic compounds in the management of PNP, warranting the initiation of clinical trials.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ph16101363/s1>. Table S1. Description of animal models of peripheral neuropathic pain.

Author Contributions: Conceptualization, D.B.; methodology, E.M. and D.B.; software, E.M. and D.B.; validation, E.M. and D.B.; formal analysis, E.M. and D.B.; investigation, E.M. and D.B.; resources, D.B.; data curation, E.M. and D.B.; writing—original draft preparation, E.M. and D.B.; writing—review and editing, E.M. and D.B.; visualization, E.M. and D.B.; supervision, D.B.; project administration, D.B.; funding acquisition, D.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by International Research Centre 3: European Centre for Health and Human Mobility—Clermont Auvergne University. The APC was funded by CHU Clermont-Ferrand.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing is not applicable.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

- Raja, S.N.; Carr, D.B.; Cohen, M.; Finnerup, N.B.; Flor, H.; Gibson, S.; Keefe, F.J.; Mogil, J.S.; Ringkamp, M.; Sluka, K.A.; et al. The Revised International Association for the Study of Pain Definition of Pain: Concepts, Challenges, and Compromises. *Pain* **2020**, *161*, 1976–1982. [[CrossRef](#)] [[PubMed](#)]
- Murphy, D.; Lester, D.; Clay Smither, F.; Balakhanlou, E. Peripheral Neuropathic Pain. *NeuroRehabilitation* **2020**, *47*, 265–283. [[CrossRef](#)] [[PubMed](#)]
- Meacham, K.; Shepherd, A.; Mohapatra, D.P.; Haroutounian, S. Neuropathic Pain: Central vs. Peripheral Mechanisms. *Curr. Pain Headache Rep.* **2017**, *21*, 28. [[CrossRef](#)]
- van Hecke, O.; Austin, S.K.; Khan, R.A.; Smith, B.H.; Torrance, N. Neuropathic Pain in the General Population: A Systematic Review of Epidemiological Studies. *Pain* **2014**, *155*, 654–662. [[CrossRef](#)]
- Finnerup, N.B.; Attal, N.; Haroutounian, S.; McNicol, E.; Baron, R.; Dworkin, R.H.; Gilron, I.; Haanpää, M.; Hansson, P.; Jensen, T.S.; et al. Pharmacotherapy for Neuropathic Pain in Adults: A Systematic Review and Meta-Analysis. *Lancet Neurol.* **2015**, *14*, 162–173. [[CrossRef](#)]
- Cuménal, M.; Selvy, M.; Kerckhove, N.; Bertin, C.; Morez, M.; Courteix, C.; Busserolles, J.; Balaýssac, D. The Safety of Medications Used to Treat Peripheral Neuropathic Pain, Part 2 (Opioids, Cannabinoids and Other Drugs): Review of Double-Blind, Placebo-Controlled, Randomized Clinical Trials. *Expert Opin. Drug Saf.* **2021**, *20*, 51–68. [[CrossRef](#)]
- Selvy, M.; Cuménal, M.; Kerckhove, N.; Courteix, C.; Busserolles, J.; Balaýssac, D. The Safety of Medications Used to Treat Peripheral Neuropathic Pain, Part 1 (Antidepressants and Antiepileptics): Review of Double-Blind, Placebo-Controlled, Randomized Clinical Trials. *Expert Opin. Drug Saf.* **2020**, *19*, 707–733. [[CrossRef](#)]
- Finnerup, N.B.; Kuner, R.; Jensen, T.S. Neuropathic Pain: From Mechanisms to Treatment. *Physiol. Rev.* **2021**, *101*, 259–301. [[CrossRef](#)] [[PubMed](#)]
- Torrance, N.; Ferguson, J.A.; Afolabi, E.; Bennett, M.I.; Serpell, M.G.; Dunn, K.M.; Smith, B.H. Neuropathic Pain in the Community: More under-Treated than Refractory? *Pain* **2013**, *154*, 690–699. [[CrossRef](#)]
- Naser, P.V.; Kuner, R. Molecular, Cellular and Circuit Basis of Cholinergic Modulation of Pain. *Neuroscience* **2018**, *387*, 135–148. [[CrossRef](#)]
- Colangelo, C.; Shichkova, P.; Keller, D.; Markram, H.; Ramaswamy, S. Cellular, Synaptic and Network Effects of Acetylcholine in the Neocortex. *Front. Neural Circuits* **2019**, *13*, 24. [[CrossRef](#)]
- Elgoyhen, A.B. The A9 α 10 Acetylcholine Receptor: A Non-Neuronal Nicotinic Receptor. *Pharmacol. Res.* **2023**, *190*, 106735. [[CrossRef](#)]
- Hone, A.J.; McIntosh, J.M. Nicotinic Acetylcholine Receptors: Therapeutic Targets for Novel Ligands to Treat Pain and Inflammation. *Pharmacol. Res.* **2023**, *190*, 106715. [[CrossRef](#)] [[PubMed](#)]
- Ho, T.N.T.; Abraham, N.; Lewis, R.J. Structure-Function of Neuronal Nicotinic Acetylcholine Receptor Inhibitors Derived From Natural Toxins. *Front. Neurosci.* **2020**, *14*, 609005. [[CrossRef](#)]

15. Picciotto, M.R.; Higley, M.J.; Mineur, Y.S. Acetylcholine as a Neuromodulator: Cholinergic Signaling Shapes Nervous System Function and Behavior. *Neuron* **2012**, *76*, 116–129. [[CrossRef](#)] [[PubMed](#)]
16. Zhuo, M.; Gebhart, G.F. Tonic Cholinergic Inhibition of Spinal Mechanical Transmission. *Pain* **1991**, *46*, 211–222. [[CrossRef](#)] [[PubMed](#)]
17. Matsumoto, M.; Xie, W.; Inoue, M.; Ueda, H. Evidence for the Tonic Inhibition of Spinal Pain by Nicotinic Cholinergic Transmission through Primary Afferents. *Mol. Pain* **2007**, *3*. [[CrossRef](#)]
18. Rashid, M.H.; Ueda, H. Neuropathy-Specific Analgesic Action of Intrathecal Nicotinic Agonists and Its Spinal GABA-Mediated Mechanism. *Brain Res.* **2002**, *953*, 53–62. [[CrossRef](#)]
19. Fiorino, D.F.; Garcia-Guzman, M. Muscarinic Pain Pharmacology: Realizing the Promise of Novel Analgesics by Overcoming Old Challenges. In *Muscarinic Receptors*; Fryer, A.D., Christopoulos, A., Nathanson, N.M., Eds.; Handbook of Experimental Pharmacology; Springer: Berlin/Heidelberg, Germany, 2012; Volume 208, pp. 191–221, ISBN 978-3-642-23273-2.
20. Kimura, M.; Hayashida, K.; Eisenach, J.C.; Saito, S.; Obata, H. Relief of Hypersensitivity after Nerve Injury from Systemic Donepezil Involves Spinal Cholinergic and γ -Aminobutyric Acid Mechanisms. *Anesthesiology* **2013**, *118*, 173–180. [[CrossRef](#)]
21. Yoon, S.; Kwon, Y.; Kim, H.; Roh, D.; Kang, S.; Kim, C.; Han, H.; Kim, K.; Yang, I.; Beitz, A. Intrathecal Neostigmine Reduces the Zymosan-Induced Inflammatory Response in a Mouse Air Pouch Model via Adrenomedullary Activity: Involvement of Spinal Muscarinic Type 2 Receptors. *Neuropharmacology* **2005**, *49*, 275–282. [[CrossRef](#)]
22. Cai, Y.; Chen, S.; Han, H.; Sood, A.K.; Lopez-Berestein, G.; Pan, H. Role of M₂, M₃, and M₄ Muscarinic Receptor Subtypes in the Spinal Cholinergic Control of Nociception Revealed Using siRNA in Rats. *J. Neurochem.* **2009**, *111*, 1000–1010. [[CrossRef](#)] [[PubMed](#)]
23. Shelukhina, I.; Paddenberg, R.; Kummer, W.; Tsetlin, V. Functional Expression and Axonal Transport of A7 nAChRs by Peptidergic Nociceptors of Rat Dorsal Root Ganglion. *Brain Struct. Funct.* **2015**, *220*, 1885–1899. [[CrossRef](#)] [[PubMed](#)]
24. Jeong, S.-G.; Choi, I.-S.; Cho, J.-H.; Jang, I.-S. Cholinergic Modulation of Primary Afferent Glutamatergic Transmission in Rat Medullary Dorsal Horn Neurons. *Neuropharmacology* **2013**, *75*, 295–303. [[CrossRef](#)] [[PubMed](#)]
25. Zhang, H.-M.; Chen, S.-R.; Pan, H.-L. Regulation of Glutamate Release From Primary Afferents and Interneurons in the Spinal Cord by Muscarinic Receptor Subtypes. *J. Neurophysiol.* **2007**, *97*, 102–109. [[CrossRef](#)] [[PubMed](#)]
26. Chen, S.-R.; Chen, H.; Yuan, W.-X.; Wess, J.; Pan, H.-L. Differential Regulation of Primary Afferent Input to Spinal Cord by Muscarinic Receptor Subtypes Delineated Using Knockout Mice. *J. Biol. Chem.* **2014**, *289*, 14321–14330. [[CrossRef](#)]
27. Iwamoto, E.T.; Marion, L. Adrenergic, Serotonergic and Cholinergic Components of Nicotinic Antinociception in Rats. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 777–789.
28. Jarczyk, F.J.; White, S.R.; Hammond, D.L. Plasticity in Brainstem Mechanisms of Pain Modulation by Nicotinic Acetylcholine Receptors in the Rat. *eNeuro* **2017**, *4*, 1–16. [[CrossRef](#)]
29. Stornetta, R.L.; Macon, C.J.; Nguyen, T.M.; Coates, M.B.; Guyenet, P.G. Cholinergic Neurons in the Mouse Rostral Ventrolateral Medulla Target Sensory Afferent Areas. *Brain Struct. Funct.* **2013**, *218*, 455–475. [[CrossRef](#)] [[PubMed](#)]
30. Tricco, A.C.; Lillie, E.; Zarin, W.; O'Brien, K.K.; Colquhoun, H.; Levac, D.; Moher, D.; Peters, M.D.J.; Horsley, T.; Weeks, L.; et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* **2018**, *169*, 467–473. [[CrossRef](#)]
31. Kimura, M.; Saito, S.; Obata, H. Dexmedetomidine Decreases Hyperalgesia in Neuropathic Pain by Increasing Acetylcholine in the Spinal Cord. *Neurosci. Lett.* **2012**, *529*, 70–74. [[CrossRef](#)] [[PubMed](#)]
32. Ferrier, J.; Bayet-Robert, M.; Dalmann, R.; El Guerrab, A.; Aissouni, Y.; Graveron-Demilly, D.; Chalus, M.; Pinguet, J.; Eschaliier, A.; Richard, D.; et al. Cholinergic Neurotransmission in the Posterior Insular Cortex Is Altered in Preclinical Models of Neuropathic Pain: Key Role of Muscarinic M₂ Receptors in Donepezil-Induced Antinociception. *J. Neurosci.* **2015**, *35*, 16418–16430. [[CrossRef](#)]
33. Selvy, M.; Mattévi, C.; Dalbos, C.; Aissouni, Y.; Chapuy, E.; Martin, P.-Y.; Collin, A.; Richard, D.; Dumontet, C.; Busserolles, J.; et al. Analgesic and Preventive Effects of Donepezil in Animal Models of Chemotherapy-Induced Peripheral Neuropathy: Involvement of Spinal Muscarinic Acetylcholine M₂ Receptors. *Biomed. Pharmacother.* **2022**, *149*, 112915. [[CrossRef](#)]
34. Zuo, Z.-X.; Wang, Y.-J.; Liu, L.; Wang, Y.; Mei, S.-H.; Feng, Z.-H.; Wang, M.; Li, X.-Y. Huperzine A Alleviates Mechanical Allodynia but Not Spontaneous Pain via Muscarinic Acetylcholine Receptors in Mice. *Neural Plast.* **2015**, *2015*, 453170. [[CrossRef](#)] [[PubMed](#)]
35. Dhanasobhon, D.; Medrano, M.-C.; Becker, L.J.; Moreno-Lopez, Y.; Kavraal, S.; Bichara, C.; Schlichter, R.; Inquimbert, P.; Yalcin, I.; Cordero-Erausquin, M. Enhanced Analgesic Cholinergic Tone in the Spinal Cord in a Mouse Model of Neuropathic Pain. *Neurobiol. Dis.* **2021**, *155*, 105363. [[CrossRef](#)] [[PubMed](#)]
36. Paqueron, X.; Li, X.; Eisenach, J.C. P75-Expressing Elements Are Necessary for Anti-Allodynic Effects of Spinal Clonidine and Neostigmine. *Neuroscience* **2001**, *102*, 681–686. [[CrossRef](#)]
37. Chen, S.R.; Khan, G.M.; Pan, H.L. Antiallodynic Effect of Intrathecal Neostigmine Is Mediated by Spinal Nitric Oxide in a Rat Model of Diabetic Neuropathic Pain. *Anesthesiology* **2001**, *95*, 1007–1012. [[CrossRef](#)]
38. Takasu, K.; Honda, M.; Ono, H.; Tanabe, M. Spinal Alpha(2)-Adrenergic and Muscarinic Receptors and the NO Release Cascade Mediate Supraspinally Produced Effectiveness of Gabapentin at Decreasing Mechanical Hypersensitivity in Mice after Partial Nerve Injury. *Br. J. Pharmacol.* **2006**, *148*, 233–244. [[CrossRef](#)] [[PubMed](#)]
39. Marinelli, S.; Vacca, V.; Ricordy, R.; Ugenti, C.; Tata, A.M.; Luvisetto, S.; Pavone, F. The Analgesic Effect on Neuropathic Pain of Retrogradely Transported Botulinum Neurotoxin A Involves Schwann Cells and Astrocytes. *PLoS ONE* **2012**, *7*, e47977. [[CrossRef](#)]

40. Favre-Guilmard, C.; Auguet, M.; Chabrier, P.-E. Different Antinociceptive Effects of Botulinum Toxin Type A in Inflammatory and Peripheral Polyneuropathic Rat Models. *Eur. J. Pharmacol.* **2009**, *617*, 48–53. [[CrossRef](#)]
41. Emril, D.R.; Wibowo, S.; Meliala, L.; Susilowati, R. Cytidine 5'-Diphosphocholine Administration Prevents Peripheral Neuropathic Pain after Sciatic Nerve Crush Injury in Rats. *J. Pain Res.* **2016**, *9*, 287–291. [[CrossRef](#)]
42. Bagdas, D.; Sonat, F.A.; Hamurtekin, E.; Sonal, S.; Gurun, M.S. The Antihyperalgesic Effect of Cytidine-5'-Diphosphate-Choline in Neuropathic and Inflammatory Pain Models. *Behav. Pharmacol.* **2011**, *22*, 589–598. [[CrossRef](#)]
43. Kanat, O.; Bagdas, D.; Ozboluk, H.Y.; Gurun, M.S. Preclinical Evidence for the Antihyperalgesic Activity of CDP-Choline in Oxaliplatin-Induced Neuropathic Pain. *J. BUON* **2013**, *18*, 1012–1018.
44. Kyte, S.L.; Toma, W.; Bagdas, D.; Meade, J.A.; Schurman, L.D.; Lichtman, A.H.; Chen, Z.-J.; Del Fabbro, E.; Fang, X.; Bigbee, J.W.; et al. Nicotine Prevents and Reverses Paclitaxel-Induced Mechanical Allodynia in a Mouse Model of CIPN. *J. Pharmacol. Exp. Ther.* **2018**, *364*, 110–119. [[CrossRef](#)] [[PubMed](#)]
45. Bagdas, D.; Ergun, D.; Jackson, A.; Toma, W.; Schulte, M.K.; Damaj, M.I. Allosteric Modulation of A4 β 2* Nicotinic Acetylcholine Receptors: Desformylflustrabromine Potentiates Antiallodynic Response of Nicotine in a Mouse Model of Neuropathic Pain. *Eur. J. Pain* **2018**, *22*, 84–93. [[CrossRef](#)]
46. Abdin, M.J.; Morioka, N.; Morita, K.; Kitayama, T.; Kitayama, S.; Nakashima, T.; Dohi, T. Analgesic Action of Nicotine on Tibial Nerve Transection (TNT)-Induced Mechanical Allodynia through Enhancement of the Glycinergic Inhibitory System in Spinal Cord. *Life Sci.* **2006**, *80*, 9–16. [[CrossRef](#)]
47. Kiguchi, N.; Kobayashi, Y.; Maeda, T.; Tominaga, S.; Nakamura, J.; Fukazawa, Y.; Ozaki, M.; Kishioka, S. Activation of Nicotinic Acetylcholine Receptors on Bone Marrow-Derived Cells Relieves Neuropathic Pain Accompanied by Peripheral Neuroinflammation. *Neurochem. Int.* **2012**, *61*, 1212–1219. [[CrossRef](#)]
48. Young, T.; Wittenauer, S.; Parker, R.; Vincler, M. Peripheral Nerve Injury Alters Spinal Nicotinic Acetylcholine Receptor Pharmacology. *Eur. J. Pharmacol.* **2008**, *590*, 163–169. [[CrossRef](#)]
49. Wieskopf, J.S.; Mathur, J.; Limapichat, W.; Post, M.R.; Al-Qazzaz, M.; Sorge, R.E.; Martin, L.J.; Zaykin, D.V.; Smith, S.B.; Freitas, K.; et al. The Nicotinic A6 Subunit Gene Determines Variability in Chronic Pain Sensitivity via Cross-Inhibition of P2X2/3 Receptors. *Sci. Transl. Med.* **2015**, *7*, 287ra72. [[CrossRef](#)] [[PubMed](#)]
50. Josiah, D.T.; Vincler, M.A. Impact of Chronic Nicotine on the Development and Maintenance of Neuropathic Hypersensitivity in the Rat. *Psychopharmacology* **2006**, *188*, 152–161. [[CrossRef](#)]
51. Xanthos, D.N.; Beiersdorf, J.W.; Thrun, A.; Ianosi, B.; Orr-Urtreger, A.; Huck, S.; Scholze, P. Role of A5-Containing Nicotinic Receptors in Neuropathic Pain and Response to Nicotine. *Neuropharmacology* **2015**, *95*, 37–49. [[CrossRef](#)]
52. Brunori, G.; Schoch, J.; Mercatelli, D.; Ozawa, A.; Toll, L.; Cippitelli, A. Influence of Neuropathic Pain on Nicotinic Acetylcholine Receptor Plasticity and Behavioral Responses to Nicotine in Rats. *Pain* **2018**, *159*, 2179–2191. [[CrossRef](#)] [[PubMed](#)]
53. Saika, F.; Kiguchi, N.; Kobayashi, Y.; Kishioka, S. Peripheral Alpha4beta2 Nicotinic Acetylcholine Receptor Signalling Attenuates Tactile Allodynia and Thermal Hyperalgesia after Nerve Injury in Mice. *Acta Physiol. (Oxf.)* **2015**, *213*, 462–471. [[CrossRef](#)]
54. Holtman, J.R.; Crooks, P.A.; Johnson-Hardy, J.K.; Wala, E.P. The Analgesic and Toxic Effects of Nornicotinic Enantiomers Alone and in Interaction with Morphine in Rodent Models of Acute and Persistent Pain. *Pharmacol. Biochem. Behav.* **2010**, *94*, 352–362. [[CrossRef](#)] [[PubMed](#)]
55. Kesingland, A.C.; Gentry, C.T.; Panesar, M.S.; Bowes, M.A.; Vernier, J.M.; Cube, R.; Walker, K.; Urban, L. Analgesic Profile of the Nicotinic Acetylcholine Receptor Agonists, (+)-Epibatidine and ABT-594 in Models of Persistent Inflammatory and Neuropathic Pain. *Pain* **2000**, *86*, 113–118. [[CrossRef](#)] [[PubMed](#)]
56. Kiguchi, N.; Kobayashi, D.; Saika, F.; Matsuzaki, S.; Kishioka, S. Inhibition of Peripheral Macrophages by Nicotinic Acetylcholine Receptor Agonists Suppresses Spinal Microglial Activation and Neuropathic Pain in Mice with Peripheral Nerve Injury. *J. Neuroinflamm.* **2018**, *15*, 96. [[CrossRef](#)] [[PubMed](#)]
57. Ueda, M.; Iida, Y.; Yoneyama, T.; Kawai, T.; Ogawa, M.; Magata, Y.; Saji, H. In Vivo Relationship between Thalamic Nicotinic Acetylcholine Receptor Occupancy Rates and Antiallodynic Effects in a Rat Model of Neuropathic Pain: Persistent Agonist Binding Inhibits the Expression of Antiallodynic Effects. *Synapse* **2011**, *65*, 77–83. [[CrossRef](#)]
58. Li, W.; Cai, J.; Wang, B.H.; Huang, L.; Fan, J.; Wang, Y. Antinociceptive Effects of Novel Epibatidine Analogs through Activation of A4 β 2 Nicotinic Receptors. *Sci. China Life Sci.* **2018**, *61*, 688–695. [[CrossRef](#)]
59. Lynch, J.J.; Wade, C.L.; Mikusa, J.P.; Decker, M.W.; Honore, P. ABT-594 (a Nicotinic Acetylcholine Agonist): Anti-Allodynia in a Rat Chemotherapy-Induced Pain Model. *Eur. J. Pharmacol.* **2005**, *509*, 43–48. [[CrossRef](#)]
60. Saika, F.; Kiguchi, N.; Matsuzaki, S.; Kobayashi, D.; Kishioka, S. Inflammatory Macrophages in the Sciatic Nerves Facilitate Neuropathic Pain Associated with Type 2 Diabetes Mellitus. *J. Pharmacol. Exp. Ther.* **2019**, *368*, 535–544. [[CrossRef](#)]
61. Yoon, H.; Kim, M.J.; Yoon, I.; Li, D.X.; Bae, H.; Kim, S.K. Nicotinic Acetylcholine Receptors Mediate the Suppressive Effect of an Injection of Diluted Bee Venom into the GV3 Acupoint on Oxaliplatin-Induced Neuropathic Cold Allodynia in Rats. *Biol. Pharm. Bull.* **2015**, *38*, 710–714. [[CrossRef](#)]
62. Cheng, L.-Z.; Han, L.; Fan, J.; Huang, L.-T.; Peng, L.-C.; Wang, Y. Enhanced Inhibitory Synaptic Transmission in the Spinal Dorsal Horn Mediates Antinociceptive Effects of TC-2559. *Mol. Pain* **2011**, *7*, 56. [[CrossRef](#)] [[PubMed](#)]
63. Ueda, M.; Iida, Y.; Tominaga, A.; Yoneyama, T.; Ogawa, M.; Magata, Y.; Nishimura, H.; Kuge, Y.; Saji, H. Nicotinic Acetylcholine Receptors Expressed in the Ventralposterolateral Thalamic Nucleus Play an Important Role in Anti-Allodynic Effects. *Br. J. Pharmacol.* **2010**, *159*, 1201–1210. [[CrossRef](#)] [[PubMed](#)]

64. Ji, J.; Bunnelle, W.H.; Anderson, D.J.; Faltynek, C.; Dyhring, T.; Ahring, P.K.; Rueter, L.E.; Curzon, P.; Buckley, M.J.; Marsh, K.C.; et al. A-366833: A Novel Nicotinonitrile-Substituted 3,6-Diazabicyclo[3.2.0]-Heptane Alpha4beta2 Nicotinic Acetylcholine Receptor Selective Agonist: Synthesis, Analgesic Efficacy and Tolerability Profile in Animal Models. *Biochem. Pharmacol.* **2007**, *74*, 1253–1262. [[CrossRef](#)] [[PubMed](#)]
65. Nirogi, R.; Jabaris, S.L.; Jayarajan, P.; Abraham, R.; Shanmuganathan, D.; Rasheed, M.A.; Royapalley, P.K.; Goura, V. Antinociceptive Activity of A4β2* Neuronal Nicotinic Receptor Agonist A-366833 in Experimental Models of Neuropathic and Inflammatory Pain. *Eur. J. Pharmacol.* **2011**, *668*, 155–162. [[CrossRef](#)]
66. Rueter, L.E.; Kohlhaas, K.L.; Curzon, P.; Surowy, C.S.; Meyer, M.D. Peripheral and Central Sites of Action for A-85380 in the Spinal Nerve Ligation Model of Neuropathic Pain. *Pain* **2003**, *103*, 269–276. [[CrossRef](#)] [[PubMed](#)]
67. Lee, C.-H.; Zhu, C.; Malysz, J.; Campbell, T.; Shaughnessy, T.; Honore, P.; Polakowski, J.; Gopalakrishnan, M. A4β2 Neuronal Nicotinic Receptor Positive Allosteric Modulation: An Approach for Improving the Therapeutic Index of A4β2 nAChR Agonists in Pain. *Biochem. Pharmacol.* **2011**, *82*, 959–966. [[CrossRef](#)] [[PubMed](#)]
68. Gong, S.; Liang, Q.; Zhu, Q.; Ding, D.; Yin, Q.; Tao, J.; Jiang, X. Nicotinic Acetylcholine Receptor A7 Subunit Is Involved in the Cobratoxin-Induced Antinociception in an Animal Model of Neuropathic Pain. *Toxicol.* **2015**, *93*, 31–36. [[CrossRef](#)]
69. Freitas, K.; Ghosh, S.; Ivy Carroll, F.; Lichtman, A.H.; Imad Damaj, M. Effects of A7 Positive Allosteric Modulators in Murine Inflammatory and Chronic Neuropathic Pain Models. *Neuropharmacology* **2013**, *65*, 156–164. [[CrossRef](#)] [[PubMed](#)]
70. Di Cesare Mannelli, L.; Pacini, A.; Matera, C.; Zanardelli, M.; Mello, T.; De Amici, M.; Dallanoce, C.; Ghelardini, C. Involvement of A7 nAChR Subtype in Rat Oxaliplatin-Induced Neuropathy: Effects of Selective Activation. *Neuropharmacology* **2014**, *79*, 37–48. [[CrossRef](#)]
71. Ji, L.; Chen, Y.; Wei, H.; Feng, H.; Chang, R.; Yu, D.; Wang, X.; Gong, X.; Zhang, M. Activation of Alpha7 Acetylcholine Receptors Reduces Neuropathic Pain by Decreasing Dynorphin A Release from Microglia. *Brain Res.* **2019**, *1715*, 57–65. [[CrossRef](#)]
72. Bagdas, D.; Wilkerson, J.L.; Kulkarni, A.; Toma, W.; AlSharari, S.; Gul, Z.; Lichtman, A.H.; Papke, R.L.; Thakur, G.A.; Damaj, M.I. The A7 Nicotinic Receptor Dual Allosteric Agonist and Positive Allosteric Modulator GAT107 Reverses Nociception in Mouse Models of Inflammatory and Neuropathic Pain. *Br. J. Pharmacol.* **2016**, *173*, 2506–2520. [[CrossRef](#)]
73. Arias, H.R.; Ghelardini, C.; Lucarini, E.; Tae, H.-S.; Yousuf, A.; Marcovich, I.; Manetti, D.; Romanelli, M.N.; Elgoyhen, A.B.; Adams, D.J.; et al. (E)-3-Furan-2-Yl-N-p-Tolyl-Acrylamide and Its Derivative DM489 Decrease Neuropathic Pain in Mice Predominantly by A7 Nicotinic Acetylcholine Receptor Potentiation. *ACS Chem. Neurosci.* **2020**, *11*, 3603–3614. [[CrossRef](#)]
74. Bagdas, D.; Sevdar, G.; Gul, Z.; Younis, R.; Cavun, S.; Tae, H.-S.; Ortells, M.O.; Arias, H.R.; Gurun, M.S. (E)-3-Furan-2-Yl-N-Phenylacrylamide (PAM-4) Decreases Nociception and Emotional Manifestations of Neuropathic Pain in Mice by A7 Nicotinic Acetylcholine Receptor Potentiation. *Neurol. Res.* **2021**, *43*, 1056–1068. [[CrossRef](#)] [[PubMed](#)]
75. Pacini, A.; Di Cesare Mannelli, L.; Bonaccini, L.; Ronzoni, S.; Bartolini, A.; Ghelardini, C. Protective Effect of Alpha7 nAChR: Behavioural and Morphological Features on Neuropathy. *Pain* **2010**, *150*, 542–549. [[CrossRef](#)]
76. Loram, L.C.; Taylor, F.R.; Strand, K.A.; Maier, S.F.; Speake, J.D.; Jordan, K.G.; James, J.W.; Wene, S.P.; Pritchard, R.C.; Green, H.; et al. Systemic Administration of an Alpha-7 Nicotinic Acetylcholine Agonist Reverses Neuropathic Pain in Male Sprague Dawley Rats. *J. Pain* **2012**, *13*, 1162–1171. [[CrossRef](#)] [[PubMed](#)]
77. Papke, R.L.; Bagdas, D.; Kulkarni, A.R.; Gould, T.; AlSharari, S.D.; Thakur, G.A.; Damaj, M.I. The Analgesic-like Properties of the Alpha7 nAChR Silent Agonist NS6740 Is Associated with Non-Conducting Conformations of the Receptor. *Neuropharmacology* **2015**, *91*, 34–42. [[CrossRef](#)]
78. Toma, W.; Kyte, S.L.; Bagdas, D.; Jackson, A.; Meade, J.A.; Rahman, F.; Chen, Z.-J.; Del Fabbro, E.; Cantwell, L.; Kulkarni, A.; et al. The A7 Nicotinic Receptor Silent Agonist R-47 Prevents and Reverses Paclitaxel-Induced Peripheral Neuropathy in Mice without Tolerance or Altering Nicotine Reward and Withdrawal. *Exp. Neurol.* **2019**, *320*, 113010. [[CrossRef](#)]
79. Bagdas, D.; Targowska-Duda, K.M.; López, J.J.; Perez, E.G.; Arias, H.R.; Damaj, M.I. The Antinociceptive and Antiinflammatory Properties of 3-Furan-2-Yl-N-p-Tolyl-Acrylamide, a Positive Allosteric Modulator of A7 Nicotinic Acetylcholine Receptors in Mice. *Anesth. Analg.* **2015**, *121*, 1369–1377. [[CrossRef](#)]
80. Liu, Z.; Bartels, P.; Sadeghi, M.; Du, T.; Dai, Q.; Zhu, C.; Yu, S.; Wang, S.; Dong, M.; Sun, T.; et al. A Novel α-Conopeptide Eu1.6 Inhibits N-Type (CaV2.2) Calcium Channels and Exhibits Potent Analgesic Activity. *Sci. Rep.* **2018**, *8*, 1004. [[CrossRef](#)] [[PubMed](#)]
81. Wang, D.; Yang, H.; Liang, Y.; Wang, X.; Du, X.; Li, R.; Jiang, Y.; Ye, J. Antinociceptive Effect of Spirocyclopiperazinium Salt Compound DXL-A-24 and the Underlying Mechanism. *Neurochem. Res.* **2019**, *44*, 2786–2795. [[CrossRef](#)] [[PubMed](#)]
82. Napier, I.A.; Klimis, H.; Rycroft, B.K.; Jin, A.H.; Alewood, P.F.; Motin, L.; Adams, D.J.; Christie, M.J. Intrathecal α-Conotoxins Vc1.1, Au1B and MII Acting on Distinct Nicotinic Receptor Subtypes Reverse Signs of Neuropathic Pain. *Neuropharmacology* **2012**, *62*, 2202–2207. [[CrossRef](#)]
83. Klimis, H.; Adams, D.J.; Callaghan, B.; Nevin, S.; Alewood, P.F.; Vaughan, C.W.; Mozar, C.A.; Christie, M.J. A Novel Mechanism of Inhibition of High-Voltage Activated Calcium Channels by α-Conotoxins Contributes to Relief of Nerve Injury-Induced Neuropathic Pain. *Pain* **2011**, *152*, 259–266. [[CrossRef](#)]
84. Di Cesare Mannelli, L.; Cinci, L.; Micheli, L.; Zanardelli, M.; Pacini, A.; McIntosh, J.M.; Ghelardini, C. α-Conotoxin RgIA Protects against the Development of Nerve Injury-Induced Chronic Pain and Prevents Both Neuronal and Glial Derangement. *Pain* **2014**, *155*, 1986–1995. [[CrossRef](#)] [[PubMed](#)]
85. Nevin, S.T.; Clark, R.J.; Klimis, H.; Christie, M.J.; Craik, D.J.; Adams, D.J. Are Alpha9alpha10 Nicotinic Acetylcholine Receptors a Pain Target for Alpha-Conotoxins? *Mol. Pharmacol.* **2007**, *72*, 1406–1410. [[CrossRef](#)] [[PubMed](#)]

86. Cai, F.; Xu, N.; Liu, Z.; Ding, R.; Yu, S.; Dong, M.; Wang, S.; Shen, J.; Tae, H.-S.; Adams, D.J.; et al. Targeting of N-Type Calcium Channels via GABAB-Receptor Activation by α -Conotoxin Vc1.1 Variants Displaying Improved Analgesic Activity. *J. Med. Chem.* **2018**, *61*, 10198–10205. [[CrossRef](#)] [[PubMed](#)]
87. Luo, S.; Zhangsun, D.; Harvey, P.J.; Kaas, Q.; Wu, Y.; Zhu, X.; Hu, Y.; Li, X.; Tsetlin, V.I.; Christensen, S.; et al. Cloning, Synthesis, and Characterization of AO-Conotoxin GeXIVA, a Potent A9 α 10 Nicotinic Acetylcholine Receptor Antagonist. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E4026–E4035. [[CrossRef](#)]
88. Wala, E.P.; Crooks, P.A.; McIntosh, J.M.; Holtman, J.R. Novel Small Molecule A9 α 10 Nicotinic Receptor Antagonist Prevents and Reverses Chemotherapy-Evoked Neuropathic Pain in Rats. *Anesth. Analg.* **2012**, *115*, 713–720. [[CrossRef](#)] [[PubMed](#)]
89. Holtman, J.R.; Dwoskin, L.P.; Dowell, C.; Wala, E.P.; Zhang, Z.; Crooks, P.A.; McIntosh, J.M. The Novel Small Molecule A9 α 10 Nicotinic Acetylcholine Receptor Antagonist ZZ-204G Is Analgesic. *Eur. J. Pharmacol.* **2011**, *670*, 500–508. [[CrossRef](#)]
90. Arias, H.R.; Tae, H.-S.; Micheli, L.; Yousuf, A.; Ghelardini, C.; Adams, D.J.; Di Cesare Mannelli, L. Coronaridine Congeners Decrease Neuropathic Pain in Mice and Inhibit A9 α 10 Nicotinic Acetylcholine Receptors and CaV2.2 Channels. *Neuropharmacology* **2020**, *175*, 108194. [[CrossRef](#)]
91. Liang, J.; Tae, H.-S.; Zhao, Z.; Li, X.; Zhang, J.; Chen, S.; Jiang, T.; Adams, D.J.; Yu, R. Mechanism of Action and Structure-Activity Relationship of α -Conotoxin Mr1.1 at the Human A9 α 10 Nicotinic Acetylcholine Receptor. *J. Med. Chem.* **2022**, *65*, 16204–16217. [[CrossRef](#)] [[PubMed](#)]
92. Vincler, M.; Wittenauer, S.; Parker, R.; Ellison, M.; Olivera, B.M.; McIntosh, J.M. Molecular Mechanism for Analgesia Involving Specific Antagonism of Alpha9alpha10 Nicotinic Acetylcholine Receptors. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17880–17884. [[CrossRef](#)] [[PubMed](#)]
93. Dyachenko, I.A.; Palikova, Y.A.; Palikov, V.A.; Korolkova, Y.V.; Kazakov, V.A.; Egorova, N.S.; Garifulina, A.I.; Utkin, Y.N.; Tsetlin, V.I.; Kryukova, E.V. α -Conotoxin RgIA and Oligoarginine R8 in the Mice Model Alleviate Long-Term Oxaliplatin Induced Neuropathy. *Biochimie* **2022**, *194*, 127–136. [[CrossRef](#)] [[PubMed](#)]
94. Pacini, A.; Micheli, L.; Maresca, M.; Branca, J.J.V.; McIntosh, J.M.; Ghelardini, C.; Di Cesare Mannelli, L. The A9 α 10 Nicotinic Receptor Antagonist α -Conotoxin RgIA Prevents Neuropathic Pain Induced by Oxaliplatin Treatment. *Exp. Neurol.* **2016**, *282*, 37–48. [[CrossRef](#)] [[PubMed](#)]
95. Romero, H.K.; Christensen, S.B.; Di Cesare Mannelli, L.; Gajewiak, J.; Ramachandra, R.; Elmslie, K.S.; Vetter, D.E.; Ghelardini, C.; Iadonato, S.P.; Mercado, J.L.; et al. Inhibition of A9 α 10 Nicotinic Acetylcholine Receptors Prevents Chemotherapy-Induced Neuropathic Pain. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E1825–E1832. [[CrossRef](#)] [[PubMed](#)]
96. Christensen, S.B.; Hone, A.J.; Roux, I.; Kniazeff, J.; Pin, J.-P.; Upert, G.; Servent, D.; Glowatzki, E.; McIntosh, J.M. RgIA4 Potently Blocks Mouse A9 α 10 nAChRs and Provides Long Lasting Protection against Oxaliplatin-Induced Cold Allodynia. *Front. Cell. Neurosci.* **2017**, *11*, 219. [[CrossRef](#)] [[PubMed](#)]
97. Huynh, P.N.; Christensen, S.B.; McIntosh, J.M. RgIA4 Prevention of Acute Oxaliplatin-Induced Cold Allodynia Requires A9-Containing Nicotinic Acetylcholine Receptors and CD3+ T-Cells. *Cells* **2022**, *11*, 3561. [[CrossRef](#)]
98. Huynh, P.N.; Giuvelis, D.; Christensen, S.; Tucker, K.L.; McIntosh, J.M. RgIA4 Accelerates Recovery from Paclitaxel-Induced Neuropathic Pain in Rats. *Mar. Drugs* **2019**, *18*, 12. [[CrossRef](#)]
99. Gajewiak, J.; Christensen, S.; Dowell, C.; Hararah, F.; Fisher, F.; Huynh, P.N.; Olivera, B.; McIntosh, J.M. Selective Penicillamine Substitution Enables Development of a Potent Analgesic Peptide That Acts Through a Non-Opioid Based Mechanism. *J. Med. Chem.* **2021**, *64*, 9271–9278. [[CrossRef](#)]
100. Belgi, A.; Burnley, J.V.; MacRaild, C.A.; Chhabra, S.; Elnahriry, K.A.; Robinson, S.D.; Gooding, S.G.; Tae, H.-S.; Bartels, P.; Sadeghi, M.; et al. Alkyne-Bridged α -Conotoxin Vc1.1 Potently Reverses Mechanical Allodynia in Neuropathic Pain Models. *J. Med. Chem.* **2021**, *64*, 3222–3233. [[CrossRef](#)]
101. Satkunanathan, N.; Livett, B.; Gayler, K.; Sandall, D.; Down, J.; Khalil, Z. Alpha-Conotoxin Vc1.1 Alleviates Neuropathic Pain and Accelerates Functional Recovery of Injured Neurones. *Brain Res.* **2005**, *1059*, 149–158. [[CrossRef](#)]
102. Wang, H.; Li, X.; Zhangsun, D.; Yu, G.; Su, R.; Luo, S. The A9 α 10 Nicotinic Acetylcholine Receptor Antagonist AO-Conotoxin GeXIVA[1,2] Alleviates and Reverses Chemotherapy-Induced Neuropathic Pain. *Mar. Drugs* **2019**, *17*, 265. [[CrossRef](#)]
103. Li, Z.; Han, X.; Hong, X.; Li, X.; Gao, J.; Zhang, H.; Zheng, A. Lyophilization Serves as an Effective Strategy for Drug Development of the A9 α 10 Nicotinic Acetylcholine Receptor Antagonist α -Conotoxin GeXIVA[1,2]. *Mar. Drugs* **2021**, *19*, 121. [[CrossRef](#)]
104. Li, X.; Hu, Y.; Wu, Y.; Huang, Y.; Yu, S.; Ding, Q.; Zhangsun, D.; Luo, S. Anti-Hypersensitive Effect of Intramuscular Administration of AO-Conotoxin GeXIVA[1,2] and GeXIVA[1,4] in Rats of Neuropathic Pain. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2016**, *66*, 112–119. [[CrossRef](#)] [[PubMed](#)]
105. Song, Z.; Meyerson, B.A.; Linderth, B. Muscarinic Receptor Activation Potentiates the Effect of Spinal Cord Stimulation on Pain-Related Behavior in Rats with Mononeuropathy. *Neurosci. Lett.* **2008**, *436*, 7–12. [[CrossRef](#)] [[PubMed](#)]
106. Wang, Y.-J.; Zuo, Z.-X.; Zhang, M.; Feng, Z.-H.; Yan, M.; Li, X.-Y. The Analgesic Effects of (5R,6R)6-(3-Propylthio-1,2,5-Thiadiazol-4-Yl)-1-Azabicyclo[3.2.1] Octane on a Mouse Model of Neuropathic Pain. *Anesth. Analg.* **2017**, *124*, 1330–1338. [[CrossRef](#)] [[PubMed](#)]
107. Ortega-Legaspi, J.M.; López-Avila, A.; Coffeen, U.; del Angel, R.; Pellicer, F. Scopolamine into the Anterior Cingulate Cortex Diminishes Nociception in a Neuropathic Pain Model in the Rat: An Interruption of “Nociception-Related Memory Acquisition”? *Eur. J. Pain* **2003**, *7*, 425–429. [[CrossRef](#)]

108. Koga, K.; Matsuzaki, Y.; Migita, K.; Shimoyama, S.; Eto, F.; Nakagawa, T.; Matsumoto, T.; Terada, K.; Mishima, K.; Furue, H.; et al. Stimulating Muscarinic M1 Receptors in the Anterior Cingulate Cortex Reduces Mechanical Hypersensitivity via GABAergic Transmission in Nerve Injury Rats. *Brain Res.* **2019**, *1704*, 187–195. [[CrossRef](#)] [[PubMed](#)]
109. Wood, M.W.; Martino, G.; Coupal, M.; Lindberg, M.; Schroeder, P.; Santhakumar, V.; Valiquette, M.; Sandin, J.; Widzowski, D.; Laird, J. Broad Analgesic Activity of a Novel, Selective M1 Agonist. *Neuropharmacology* **2017**, *123*, 233–241. [[CrossRef](#)]
110. Calcutt, N.A.; Smith, D.R.; Frizzi, K.; Sabbir, M.G.; Chowdhury, S.K.R.; Mixcoatl-Zecuatl, T.; Saleh, A.; Muttalib, N.; Van der Ploeg, R.; Ochoa, J.; et al. Selective Antagonism of Muscarinic Receptors Is Neuroprotective in Peripheral Neuropathy. *J. Clin. Investig.* **2017**, *127*, 608–622. [[CrossRef](#)]
111. Ghazisaeidi, S.; Muley, M.M.; Salter, M.W. Neuropathic Pain: Mechanisms, Sex Differences, and Potential Therapies for a Global Problem. *Annu. Rev. Pharmacol. Toxicol.* **2023**, *63*, 565–583. [[CrossRef](#)]
112. Mapplebeck, J.C.S.; Beggs, S.; Salter, M.W. Sex Differences in Pain: A Tale of Two Immune Cells. *Pain* **2016**, *157*, S2–S6. [[CrossRef](#)]
113. Salehi, B.; Sestito, S.; Rapposelli, S.; Peron, G.; Calina, D.; Sharifi-Rad, M.; Sharopov, F.; Martins, N.; Sharifi-Rad, J. Epibatidine: A Promising Natural Alkaloid in Health. *Biomolecules* **2018**, *9*, 6. [[CrossRef](#)]
114. Kennedy, A.C.; Belgi, A.; Husselbee, B.W.; Spanswick, D.; Norton, R.S.; Robinson, A.J. α -Conotoxin Peptidomimetics: Probing the Minimal Binding Motif for Effective Analgesia. *Toxins* **2020**, *12*, 505. [[CrossRef](#)] [[PubMed](#)]
115. Wilkerson, J.L.; Deba, F.; Crowley, M.L.; Hamouda, A.K.; McMahon, L.R. Advances in the In Vitro and In Vivo Pharmacology of Alpha4beta2 Nicotinic Receptor Positive Allosteric Modulators. *Neuropharmacology* **2020**, *168*, 108008. [[CrossRef](#)] [[PubMed](#)]
116. Bagdas, D.; Gurun, M.S.; Flood, P.; Papke, R.L.; Damaj, M.I. New Insights on Neuronal Nicotinic Acetylcholine Receptors as Targets for Pain and Inflammation: A Focus on A7 nAChRs. *Curr. Neuropharmacol.* **2018**, *16*, 415–425. [[CrossRef](#)] [[PubMed](#)]
117. Shiers, S.; Klein, R.M.; Price, T.J. Quantitative Differences in Neuronal Subpopulations between Mouse and Human Dorsal Root Ganglia Demonstrated with RNAscope in Situ Hybridization. *Pain* **2020**, *161*, 2410–2424. [[CrossRef](#)] [[PubMed](#)]
118. Umana, I.C.; Daniele, C.A.; McGehee, D.S. Neuronal Nicotinic Receptors as Analgesic Targets: It's a Winding Road. *Biochem. Pharmacol.* **2013**, *86*, 1208–1214. [[CrossRef](#)]
119. Gotti, C.; Clementi, F. Neuronal Nicotinic Receptors: From Structure to Pathology. *Prog. Neurobiol.* **2004**, *74*, 363–396. [[CrossRef](#)]
120. Del Bufalo, A.; Cesario, A.; Salinaro, G.; Fini, M.; Russo, P. Alpha9 Alpha10 Nicotinic Acetylcholine Receptors as Target for the Treatment of Chronic Pain. *Curr. Pharm. Des.* **2014**, *20*, 6042–6047. [[CrossRef](#)]
121. Ditre, J.W.; Heckman, B.W.; Zale, E.L.; Kosiba, J.D.; Maisto, S.A. Acute Analgesic Effects of Nicotine and Tobacco in Humans: A Meta-Analysis. *Pain* **2016**, *157*, 1373–1381. [[CrossRef](#)]
122. Hahn, E.J.; Rayens, M.K.; Kirsh, K.L.; Passik, S.D. Brief Report: Pain and Readiness to Quit Smoking Cigarettes. *Nicotine Tob. Res.* **2006**, *8*, 473–480. [[CrossRef](#)]
123. Pandya, A.A.; Yakel, J.L. Effects of Neuronal Nicotinic Acetylcholine Receptor Allosteric Modulators in Animal Behavior Studies. *Biochem. Pharmacol.* **2013**, *86*, 1054–1062. [[CrossRef](#)] [[PubMed](#)]
124. Tan, C.-C.; Yu, J.-T.; Wang, H.-F.; Tan, M.-S.; Meng, X.-F.; Wang, C.; Jiang, T.; Zhu, X.-C.; Tan, L. Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J. Alzheimer's Dis.* **2014**, *41*, 615–631. [[CrossRef](#)] [[PubMed](#)]
125. Hartmann-Boyce, J.; Chepkin, S.C.; Ye, W.; Bullen, C.; Lancaster, T. Nicotine Replacement Therapy versus Control for Smoking Cessation. *Cochrane Database Syst. Rev.* **2018**, *2018*, CD000146. [[CrossRef](#)] [[PubMed](#)]
126. Tonstad, S.; Arons, C.; Rollema, H.; Berlin, I.; Hajek, P.; Fagerström, K.; Els, C.; McRae, T.; Russ, C. Varenicline: Mode of Action, Efficacy, Safety and Accumulated Experience Salient for Clinical Populations. *Curr. Med. Res. Opin.* **2020**, *36*, 713–730. [[CrossRef](#)]
127. Nair, A. Publication Bias—Importance of Studies with Negative Results! *Indian J. Anaesth.* **2019**, *63*, 505. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.