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REVIEW

Acetyl-L-Carnitine in the Treatment of Peripheral Neuropathies: A Narrative Review

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ABSTRACT

Acetyl-L-carnitine is an ester of L-carnitine, both endogenous molecules, with a vital role in lipid metabolism. Exogenously delivered acetyl-L-carnitine is endowed with neuroprotective and neurotrophic actions due to its antioxidant and metabolic properties. Moreover, acetyl-L-carnitine is an epigenetic regulator of genes involved in analgesia such as the metabotropic glutamate 2 receptor in the presynaptic neurons and of neurotrophic factors including nerve growth factor. Accordingly, its long-term neurotrophic and analgesic activity has been confirmed in animal models of chronic inflammatory and neuropathic pain and in clinical studies in patients with peripheral neuropathies. The aim of this narrative review was to summarise the available evidence on the usefulness of acetyl-L-carnitine in the treatment of peripheral neuropathies.

Key Summary Points

Exogenous acetyl-l-carnitine exerts its neuroprotective and neurotrophic effects through its antioxidant and metabolic properties.

Exogenous acetyl-l-carnitine exerts its analgesic effects through the epigenetic upregulation of metabotropic glutamate 2 receptor in the presynaptic neurons, with acetyl-l-carnitine being the donor of the acetyl groups.

Studies show that treatment with acetyl-l-carnitine is effective in patients with painful peripheral polyneuropathies.

Acetyl-l-carnitine long-term neurotrophic and analgesic activity is supported by evidence from both preclinical models and clinical studies in peripheral neuropathies.

Keywords: Acetyl-L-carnitine; Neuropathic pain; Epigenetic drugs

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INTRODUCTION

L-Carnitine is an endogenous molecule biosynthesised in the human body from lysine and methionine. It is also found in several foods, with red meats, such as beef and lamb, being its richest sources. It was first isolated in 1905

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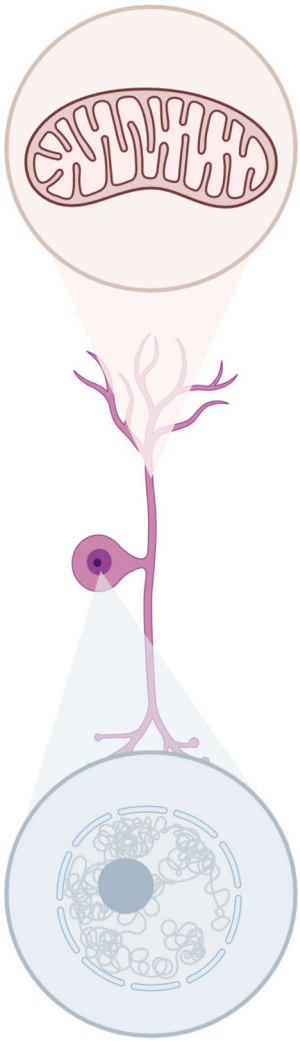

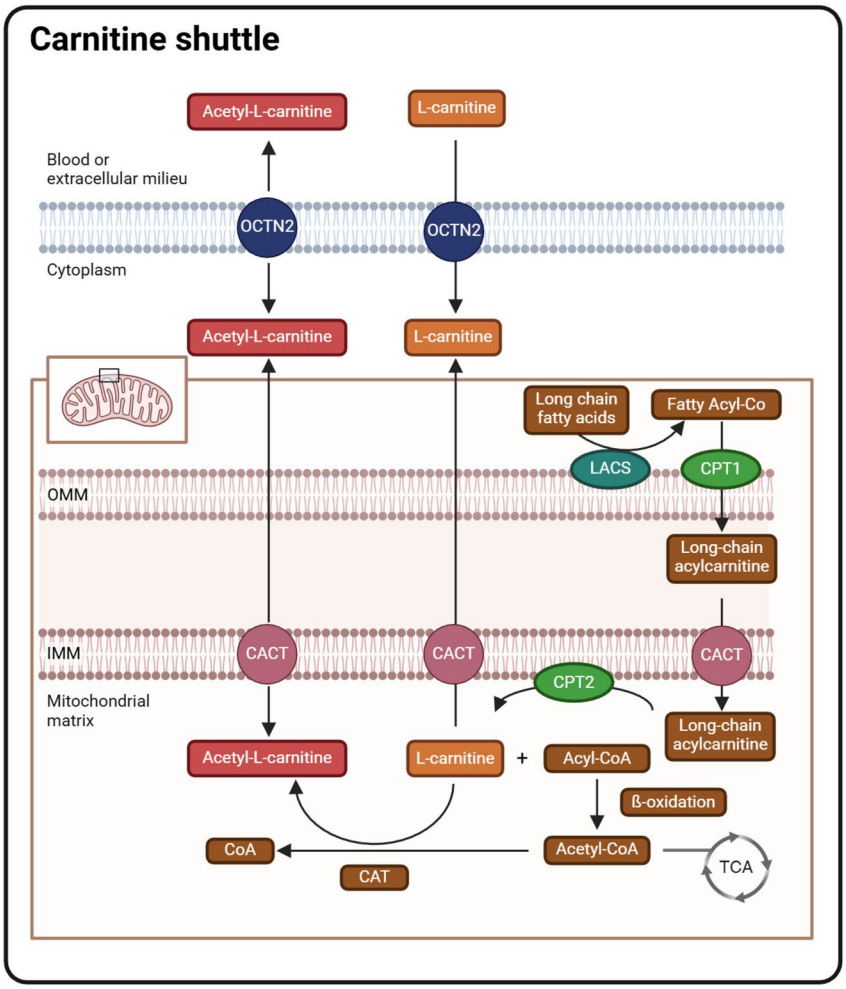
Carnitine shuttle
Acetyl-L-carnitine
L-carnitine
Blood or extracellular milieu
OCTN2
OCTN2
Cytoplasm
Acetyl-L-carnitine
L-carnitine
Long chain fatty acids
Fatty Acyl-Co
LACS
CPT1
OMM
Long-chain acylcarnitine
IMM
CACT
CACT
CACT
CPT2
Mitochondrial matrix
Long-chain acylcarnitine
Acetyl-L-carnitine
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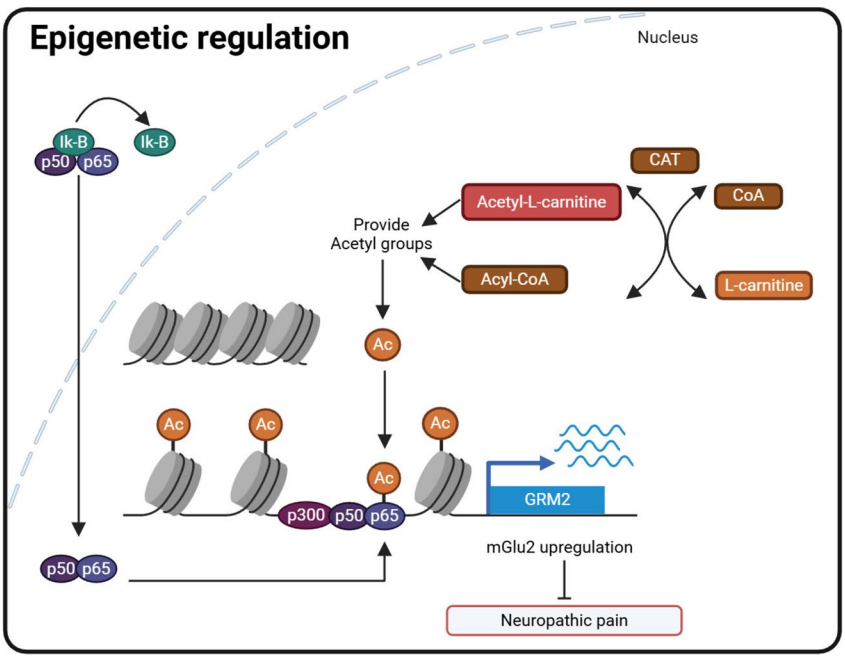
+
Acyl-CoA
ß-oxidation
CoA
Acetyl-CoA
TCA
CAT


Epigenetic regulation
Nucleus
Ik-B
Ik-B
p50
p65
CAT
Acetyl-L-carnitine
CoA
Provide Acetyl groups
Acyl-CoA
L-carnitine
Ac
Ac
Ac
Ac
Ac
p300
p50
p65
GRM2
p50
p65
mGlu2 upregulation
Neuropathic pain

◂**Fig. 1** Carnitine shuttle and epigenetic regulation exerted by acetyl-L-carnitine. Top panel. Carnitine shuttle: OCTN2 transporter transports L-carnitine and acetyl-L-carnitine into cells from the extracellular milieu and blood. In the cytosol, long-chain fatty acids are converted to fatty acyl-CoAs by LACS enzyme. Fatty acyl-CoAs are subsequently converted by CPT1 enzyme to acylcarnitines; the latter cross the IMM via the CACT transporter and are converted back to acyl-CoAs and L-carnitine by CPT2. L-Carnitine then exits the mitochondria and serves as a substrate for CPT1 to form more acylcarnitine. Carbon from acyl-CoAs in the mitochondrial matrix can be used for energy production (not shown). Bottom panel. Epigenetic mechanism of analgesia by acetyl-L-carnitine: Binding sites for NF-κB transcription factor are present in the promoter of the *GRM2* gene. Acetyl-L-carnitine induces acetylation of the p65 subunit of the NF-κB and H3 and H4 histones, thus increasing mGlu2 receptor expression and inducing analgesia. CAT, carnitine acetyltransferase; CACT, the carnitine/acylcarnitine translocase; CoA, coenzyme A; CPT1/2, carnitine palmitoyltransferase 1/2; Iκ-B, inhibitor of kappa B; IMM, inner mitochondrial membrane; LACS, long-chain acyl-CoA synthase; mGR2, metabotropic glutamate receptor 2; OCTN2, organic cation transporter 2; OMM, outer mitochondrial membrane. Created in BioRender. Tambalo, M. (2026) https://BioRender.com/3vgr1ft

from meat, hence its name from the Latin term for meat, *carnus* [1]. Acetyl-L-carnitine is an ester of L-carnitine derived by its acetylation in the mitochondria [2]. It plays a vital role in energy production by transporting fatty acids into the mitochondria, where they are metabolised [3]. The acetyl group allows acetyl-L-carnitine to cross into cells and mitochondria more easily. Acetyl-L-carnitine can also be converted back and forth to L-carnitine within the body and shuttles between cytosol and mitochondria (Fig. 1) [4].

Apart from its role in energy metabolism, multiple studies have demonstrated over the last three decades that acetyl-L-carnitine possesses neurotrophic, neuroprotective, and neuromodulatory properties. There is evidence for benefits of treatment with acetyl-L-carnitine in conditions such as neuropathy, depression, neurodegenerative disorders, and others [5, 6]. Despite this evidence, acetyl-L-carnitine is currently not approved as a drug for any indication in the United States. Instead, it is available as a dietary supplement, either alone or with other ingredients, and listed in the Dietary Supplement Label Database (DSLD) of the Office of Dietary Supplements (ODS), the lead federal US government entity for the scientific exploration of dietary supplements. ODS is part of the US National Institutes of Health [7]. In Italy, acetyl-L-carnitine is approved as a drug with an indication for treatment of mechanical and inflammatory truncal or radicular neuropathies [8]. In Australia, the permitted indications include support of nervous system health and function [9]. In addition, oral supplementation with acetyl-L-carnitine at a daily dose of 3000 mg is listed in the table of neuropathic pain treatment amongst tier 1 agents included in the Mayo Clinic guidelines on peripheral neuropathies [10].

According to the definition of the International Association for the Study of Pain (IASP), neuropathic pain is a pain that is a direct consequence of nerve damage or of a disease that involves the central or peripheral somatosensory nervous system [11]. Neuropathic pain is characterised by positive and negative symptoms in the body area innervated by the damaged neural structure. Positive symptoms include shooting or burning pain, electric-shock-like sensation, allodynia, hyperalgesia, pins and needles, or stabbing. Negative symptoms include reduced tactile and thermal sensations, numbness, hypoesthesia, or anaesthesia [12]. The pathophysiology of neuropathic pain varies and includes ectopic activity in damaged nerves or in adjacent nerves, dorsal root ganglion (DRG) or central pathways, and peripheral and central sensitisation involving numerous molecular mechanisms. All these aspects have been excellently reviewed elsewhere (e.g., [13]). Therapeutic algorithms to treat neuropathic pain include molecules acting on α2δ subunits of calcium channels, sodium channels, and descending modulatory inhibitory pathways [13].

This narrative review analyses the usefulness of acetyl-L-carnitine in the treatment of neuropathic pain.

METHODS

A non-systematic literature search was performed on PubMed using as search terms ("acetyl-L-carnitine" OR "L-acetylcarnitine" OR "ALCAR") in conjunction with one of the following: "nerve damage", "neuropathy", "peripheral neuropathy", "radiculopathy", "neuropathic pain", "diabetic polyneuropathy", "chemotherapy-induced polyneuropathy", "carpal tunnel syndrome", "Fabry disease". No filters on time of publication were applied. Further relevant references were identified by backward and forward citation searching. All available relevant studies were included.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

PHARMACODYNAMICS

Several molecular mechanisms are responsible for the pharmacological effects of acetyl-L-carnitine and are extensively reviewed in Sarzi-Puttini et al. [6]. Briefly, these include the following:

- *Neuroprotection and neurotrophic effects*. An early study showed that 250 µM acetyl-L-carnitine did not affect axon regeneration but significantly reduced the rate of death of neurons from the DRG of aging rats, suggesting its neuroprotective action [14]. This reduced rate of death in culture resulted in extended survival (up to 40 days) of rat sensory neurons in primary culture [15]. In another study, the treatment with acetyl-L-carnitine counteracted morphological alterations of neurons in a loose sciatic nerve ligation model and had a positive effect on myelin sheath function [16]. Reduced apoptosis of neurons treated with acetyl-L-carnitine in nerve regeneration studies was confirmed by a recent systematic review [17]. Many studies have documented the antioxidant properties of acetyl-L-carnitine [18–23]. For example, the treatment with acetyl-L-carnitine induced haeme oxygenase enzyme in rat astrocytes in a dose- and time-dependent fashion, heat shock protein 60 upregulation, and increased expression of the nuclear factor erythroid 2-related factor 2 transcription factor, a master regulator of antioxidant proteins [18]. Also, acetyl-L-carnitine exerts its antioxidant action through the alteration of the expression and oxidative status of a number of proteins involved in mitochondrial function and brain plasticity [23]. Other studies have demonstrated a dose-dependent effect of acetyl-L-carnitine in counteracting oxidative stress caused by arsenic and improved mitochondrial function in a rat hippocampus model and reduced the levels of free radicals induced by cuprizone in murine corpus callosum [21, 22]. Neuroprotective action was also obtained due to acetyl-L-carnitine metabolisms into pyruvate, which is a source of energy for neurons [24, 25]. In fact, carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy showed that the acetyl moiety of acetyl-L-carnitine was metabolised in both astrocytes and neurons to generate energy [25]. Lastly, acetyl-L-carnitine treatment increased the levels of nerve growth factor (NGF) in the central nervous system of old rats [26].
- *Regulation of neurotrophin expression*. In addition to its critical role in the survival of sensory neurons and neurite outgrowth, NGF signalling is also involved in nociception by activating nociceptive neurons, which express high-affinity NGF receptors [27]. Inflammation and peripheral nerve injury increase NGF expression and sensitise peripheral nociceptive terminals through the induction of gene expression in nociceptors [28]. The members of the glial cell line-derived neurotropic factor family of neurotrophins promote nerve growth and survival and normalise pain thresholds [29]. The effects of acetyl-L-carnitine on the expression of these neurotrophins in pain conditions is still debated, but an anti-hyperalgesic effect

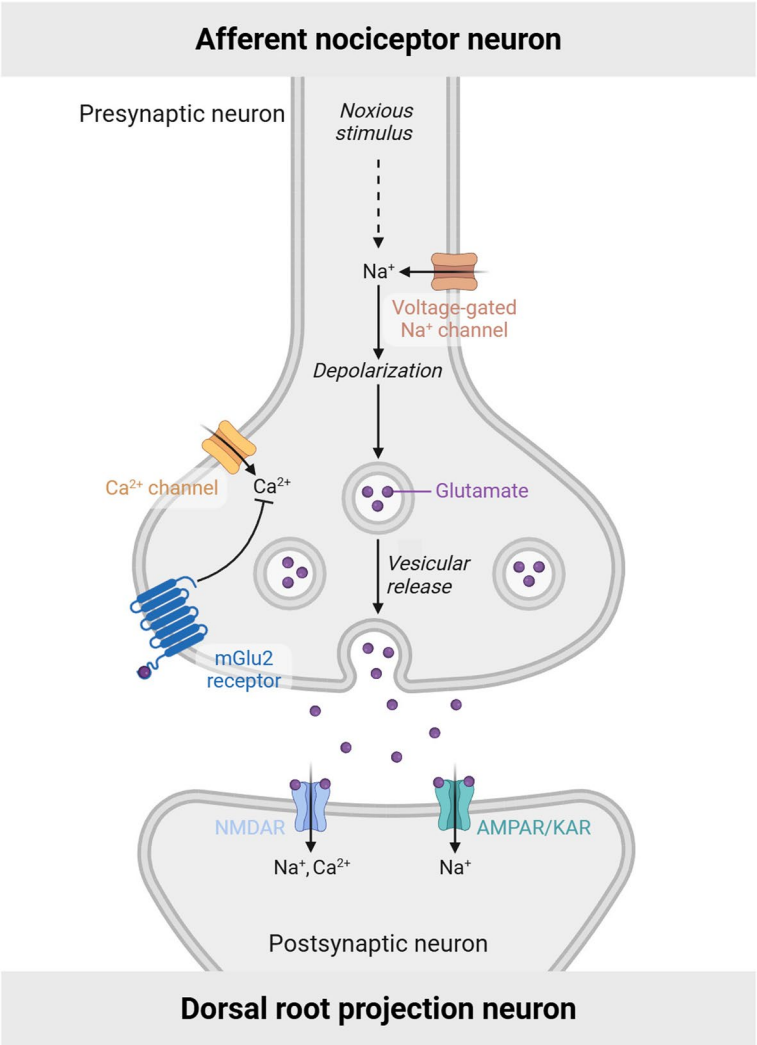


Fig. 2 Spinal nociceptive synapse with schematic representation of pain transmission from a nociceptor to dorsal horn neuron. The incoming action potential from the stimulus impulse opens the voltage-gated calcium channels (VGCC), which leads to the entry of calcium. This, in turn, triggers the release of Glu and its binding to AMPA/KA receptors and the removal of magnesium ions from NMDA receptors, which increases the flow of calcium into the post-synaptic neuron. Glutamate levels are reduced by the mGluR2 receptors. AMPAR/KAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor/kainate receptor; Glu, glutamine; NMDA, *N*-methyl-D-aspartate. Created in BioRender. Tambalo, M. (2026) https://BioRender.com/tbmd7tw. Adapted from Nashed, M. (2025). Mechanisms of Antiepileptic Drugs. Retrieved from https://app.biorender.com/biorender-templates

could derive from a better harmonisation of their activity.

- *Epigenetic effects*. Acetyl-L-carnitine is a first-in-class epigenetic regulator of genes involved in analgesic action such as the metabotropic glutamate 2 [mGlu2] receptor gene, neurotrophic factors, and antioxidant enzymes (e.g., superoxide dismutase) (Fig. 1) [30–33]. In this scenario, acetyl-L-carnitine is the donor of the acetyl groups. mGlu2 receptors regulate pain transmission by acting as a brake in the spinal nociceptive synapse (Fig. 2). Acetyl-L-carnitine-induced analgesia in neuropathic and inflammatory pain is

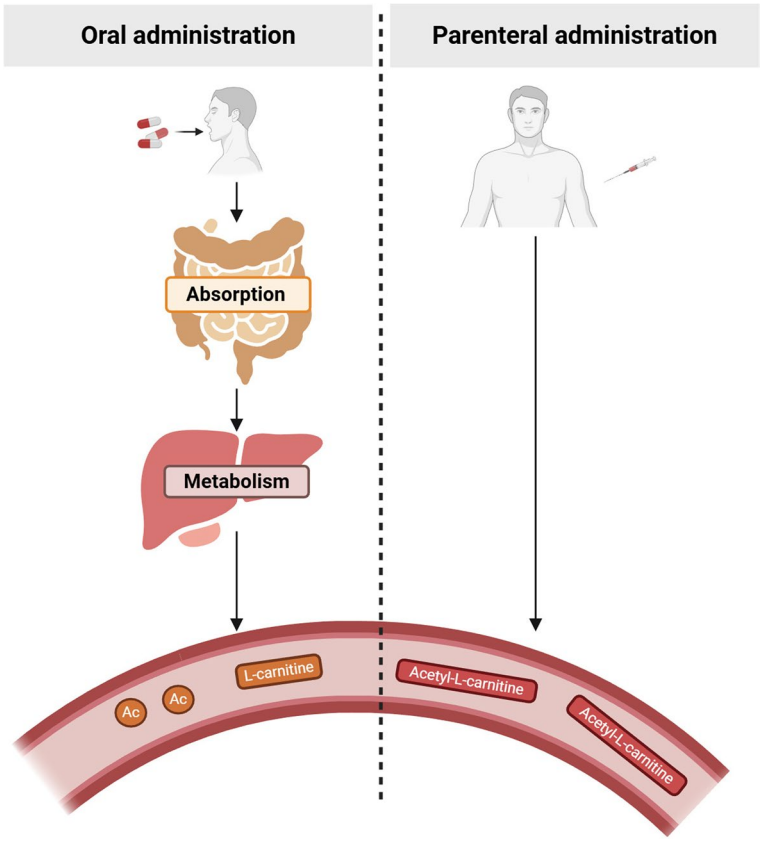


Fig. 3 Route of administration affects the pharmacokinetics of acetyl-L-carnitine. Created in BioRender. Tambalo, M. (2026) https://BioRender.com/5xponpf

long-lasting, and its duration goes beyond the time of active treatment [34, 35]. This is a known characteristic of epigenetic regulators. The role of mGlu receptor signalling in pain modulation was recently reviewed in detail [36].

- *Regulation and biosynthesis of neurotransmitters*. ^{13}C-NMR studies by Scafidi et al. revealed the incorporation of ^{13}C label from labelled acetyl-L-carnitine into glutamate and GABA neurotransmitters, suggesting that acetyl-L-carnitine was used as a substrate for their biosynthesis [25]. Similarly, acetyl-L-carnitine was found to be a precursor of acetylcholine [37]. High levels of acetyl-L-carnitine in cells capable of β-oxidation may correlate with lower levels of acetylcholine synthesis [38].

PHARMACOKINETICS

The pharmacokinetic properties of acetyl-L-carnitine differ depending on the route of administration (Fig. 3). Upon oral intake, acetyl-L-carnitine supplements are rapidly deacetylated, i.e., converted back to L-carnitine and acetyl-CoA within the intestinal wall before absorption. Acetyl-L-carnitine concentration increased by 43% after oral supplementation at a dose of 2 g/day, indicating that acetyl-L-carnitine partial absorption without hydrolysis or immediate re-acetylation also occurs [4, 39]. The half-life of acetyl-L-carnitine taken orally is ~4 h [40]. This substantial deacetylation is the reason that high plasma levels of acetyl-L-carnitine are not observed after its oral intake, unlike after parenteral administration, during which the substance bypasses the gut and enters the bloodstream

directly. Following intravenous injection of acetyl-L-carnitine, its plasma concentrations increased quickly and then declined, reaching base values within 12 h [41]. Parenteral delivery may also have implications for the safety of long-term treatment with acetyl-L-carnitine as described in the Safety section below.

Urinary excretion is the main route of elimination of acetyl-L-carnitine. As the baseline renal clearance of acetyl-L-carnitine (and L-carnitine) is substantially lower than the glomerular filtration rate, extensive (98–99%) tubular reabsorption occurs. Most of the delivered dose of acetyl-L-carnitine was recovered in the urine during the first 24 h after injection [41]. Higher doses were eliminated more rapidly [42].

ACETYL-L-CARNITINE IN THE TREATMENT OF PERIPHERAL NEUROPATHIES

Painful Radiculopathy

Important insights into the usefulness of acetyl-L-carnitine for the treatment of neuropathic pain were obtained from animal studies and are briefly summarised here. The effects of acetyl-L carnitine (compared or not to gabapentin) on compression neuropathy were studied in a rat model of sciatic nerve compression obtained through loose nerve ligation or transection [16, 43, 44]. In this model, acetyl-L-carnitine administered intraperitoneally (i.p.) at a dose of 100 mg/kg for 14 days reduced hyperalgesia and apoptosis [43, 44]. Although both acetyl-L-carnitine and gabapentin provided significant pain relief, acetyl-L-carnitine (100 mg/kg, i.p., 14 days), but not gabapentin (70 mg/kg, i.p., 14 days), significantly prevented nerve fibre and myelin thickness loss and increased axonal neurofilament immunoreactivity [16]. However, in another study, acetyl-L-carnitine therapy (50 mg/kg, i.p., 6 weeks) positively impacted the regeneration of unmyelinated fibres in the sciatic nerve based on a stereological analysis of myelinated/unmyelinated axon numbers, surface area, myelin thickness, and the myelin thickness-to-axon diameter ratio [45]. A systematic review of these data is available [17].

In parallel, several clinical studies were conducted and provided evidence that acetyl-L-carnitine may represent an effective therapeutic option for treating peripheral neuropathies (Table 1) [46–52].

The first multicentre, prospective, double-blind, placebo-controlled study to assess the usefulness of acetyl-L-carnitine in peripheral neuropathy was conducted by De Grandis et al. [46]. A total of 426 patients with peripheral sensory or motor neuropathy were included and treated with intramuscular acetyl-L-carnitine at a dose of 500 mg/twice daily for 10 days followed by 2 g/day for 20 days or placebo. Patients with sensory mono- and polyneuropathies reported a statistically significant improvement in nerve conduction velocity ($p<0.05$). In patients with motor neuropathies, a statistically significant improvement in nerve conduction velocity was observed only in those with mononeuropathies ($p<0.01$). Treatment was generally well tolerated; in fact, poor tolerability was encountered in only 3.9% of patients, whereas 1.6% discontinued treatment due to treatment-related adverse events [46]. In the subsequent non-comparative study from the same research group, 1097 patients were included. The enrolled patients suffered from peripheral mono- and polyneuropathies of various origins including entrapment, traumatic, toxic/alcoholic, diabetic, metabolic, idiopathic, vascular or infective aetiology. Neurological examination revealed improvement in all neurological indices analysed in a percentage of patients ranging from 11.9% (muscular trophism) to 29.1% (topographic score). A total of 83.1% of investigators and 84.2% of patients reported clinical efficacy, which was excellent in almost one-third of patients. In patients with reduced nerve conduction velocity, significant improvement was seen for motor and sensory nerves. Also in this study, this short-term treatment was well tolerated [48].

Onofrj et al. conducted a multicentre, double-blind, placebo-controlled study in 94 patients with painful cervical or lumbosacral neuropathies [47]. Patients were dosed with 500 mg/day or 500 mg/twice daily of intramuscular acetyl-L-carnitine or placebo for 15 days and assessed

by neurological examination (motility, reflexes), pain on visual analogue scale (VAS), superficial sensibility examination, and objective and subjective efficacy evaluation. The results showed improvements in total motility, pain VAS scores, and subjective and objective assessments of efficacy. Greater improvements were observed with the higher dose of acetyl-L-carnitine. The treatment was well tolerated [47].

In a retrospective, observational, database-based study, acetyl-L-carnitine acted synergistically with pregabalin in patients with nerve compression neuropathies [49]. This study included 81 patients with chronic compression neuropathy of the lumbosacral or cervicobrachial region divided into three homogeneous treatment arms. Twenty-seven patients received acetyl-L-carnitine at a dose of 500 mg twice daily for 10 days intramuscularly followed by the oral intake of 500 mg for 50 days (arm A); 29 patients received pregabalin at the standard dose of 150 mg three times a day (arm B); and 25 patients received a combination of acetyl-L-carnitine at a dose used in arm A plus low-dose, i.e., 150 mg/day, pregabalin (arm C) for 8 weeks and were subsequently observed for an additional 8 weeks to assess relapse latency and frequency. The combined treatment demonstrated significantly greater efficacy than standard-dose pregabalin or acetyl-L-carnitine alone, in terms of both pain symptoms measured by improvement on the VAS score (+12.8%) and neurosensory symptoms measured by the DN4 tool (+22%). Furthermore, the combined therapy was associated with better treatment adherence. Finally, the combined therapy reduced the relapse rate from 43.7% to 10.5% and more than doubled its latency, from an average of 3 weeks to an average of 7 weeks. The results in arms in A and B were similar, with a later onset of action in arm A, which is expected for epigenetic regulators [49].

Freo et al. investigated the effectiveness of acetyl-L-carnitine in 28 patients with painful radiculopathies and neuropathies, including 17 with chronic lumbar radiculopathy, unresponsive/poorly responsive to previous treatment (≤ 30% pain relief) [50, 51]. Patients initially received intramuscular acetyl-L-carnitine at a dose of 500 mg twice daily for an average of 57 ± 9 days, followed by oral administration at the same dose for up to 6 months. The primary outcome was pain intensity after 4 months of treatment. At baseline, patients reported moderate-to-severe 24-h average pain (numerical rating score; NRS ≥ 4/10), and 57% had a painDETECT score ≥ 12. Pain intensity significantly improved from baseline to month 1 of treatment (pain NRS from 7.4 ± 1.5 to 5.6 ± 1.7). At 4 months, pain improvement was moderate (30–49%) in 11 patients and substantial (≥ 50%) in eight patients. The painDETECT score decreased from 12.6 ± 6.0 at baseline to 5.0 ± 0.9 ($p < 0.01$) at 4 months of treatment. Five patients discontinued treatment due to lack of efficacy or unwillingness to continue; there were no adverse events [50].

Carpal Tunnel Syndrome

Carpal tunnel syndrome is a peripheral canalicular nerve entrapment syndrome of the upper limb. The syndrome is caused by the wrist-level compression or injury of the median nerve when it passes through a narrow carpal canal, resulting in pain and impaired function of the hand. As carpal tunnel syndrome is highly prevalent and impacts health-related quality of life in people who suffer from it, the quest for effective therapies continues [53].

Encouraging results were obtained in a study of this clinically relevant peripheral neuropathy [54]. In a multicentre, examiner-blind, clinical and neurophysiological study lasting 4 months, 120 hands from 82 patients with mild-to-moderate carpal tunnel syndrome were examined at baseline and 10, 60, and 120 days after treatment with 500 mg of acetyl-L-carnitine twice daily for 10 days intramuscularly followed by oral administration at 500 mg twice daily for 4 months. Patients underwent median nerve conduction study and were administered the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) and Neuropathic Pain Symptom Inventory (NPSI) questionnaire. The primary endpoint of the sensory conduction velocity of the median nerve was met. The treatment resulted in a significant improvement in sensory conduction velocity ($p < 0.0001$). All sensory

Table 1 Studies of acetyl-L-carnitine in patients with peripheral mononeuropathies and painful radiculopathies

Type of study [ref.]	Number of patients	Diagnosis	Acetyl-L-carnitine dosing, route of administration, treatment duration	Results
Multicentre, prospective, double-blind, placebo-controlled [46]	426	Peripheral sensory or motor neuropathy	1 g/day IM, 10 days, followed by 2 g/day IM, 20 days or placebo	Improvement in nerve conduction velocity in patients with sensory mono- and polyneuropathies ($p < 0.05$) Improvement in nerve conduction velocity in patients with motor mononeuropathies ($p < 0.01$)
Multicentre, double-blind, placebo-controlled [47]	94	Cervical or lumbosacral painful neuropathy syndrome	500 mg/day or placebo IM, 15 days 1 g/day or placebo IM, 15 days	Improvements in total motility, pain VAS scores, and subjective and objective assessments of efficacy Greater improvements with the higher dose
Multicentre, prospective, open-label, non-comparative [48]	1097	Peripheral mono- and polyneuropathies of entrapment, traumatic, toxic/alcoholic, diabetic, metabolic, idiopathic, vascular or infective origins	1 g/day IM, 10 days, followed by 2 g/day IM, 20 days	Improvements in neurological examination in up to 30% of patients (lowest for muscular trophism (11.9%), highest for topographic score (29.1%) Improvements in nerve conduction velocity Clinical efficacy perceived by 83.1% of physicians and 84.2% of patients

Table 1 continued

Type of study [ref.]	Number of patients	Diagnosis	Acetyl-L-carnitine dosing, route of administration, treatment duration	Results
Retrospective, observational, database-based [49]	81	Chronic cervical or lumbosacral neuropathy due to compression	Arm A: acetyl-L-carnitine at 500 mg/BID, IM, 10 days followed by 500 mg/BID, orally, 50 days Arm B: pregabalin at 300–600 mg/day for at least 8 weeks Arm C: acetyl-L-carnitine as in arm A + 150 mg/day of pregabalin Follow-up at 8 weeks from the end of treatment	Better pain control and improvement on DN4 score in arm C than in arms A and B Better treatment adherence in arm C than in arm A and arm B Reduced relapse rate (from 43.7% to 10.5%) and more than doubled its latency in arm C
Case series [50, 51]	28	Painful neuropathies and radiculopathies unresponsive/poorly responsive to previous treatment	500 mg/day IM for 57 ± 9 days followed by 500 mg/day orally for up to 6 months	At 1 month, pain NRS from 7.4 ± 1.5 to 5.6 ± 1.7 At 4 moths, moderate pain improvement in 11 and substantial pain improvement in 8 patients and reduction in painDETECT score from 12.6 ± 6.0 at baseline to 5.0 ± 0.9 ($p < 0.01$)
Multicentre, examiner-blind, clinical and neurophysiological study [54]	82 (120 hands)	Mild-to-moderate carpal tunnel syndrome	500 mg/BID IM, 10 days, followed by 500 mg/BID orally, 110 days	Significant improvement in the SCV ($p < 0.0001$) Significant improvements in BCTQ and NPSI (both $p < 0.0001$)

BCTQ, Boston Carpal Tunnel Syndrome Questionnaire; IM, intramuscular, NPSI, Neuropathic Pain Symptom Inventory; NRS, numerical rating scale; SCV, sensory conduction velocity; VAS, visual analogue scale; DN4, NPSI, and painDETECT, screening tools to detect neuropathic pain

neurophysiological measures improved significantly. Significant improvements in BCTQ and NPSI scores were established ($p<0.0001$) [54]. However, in a Canadian proof-of-principle, double-blind, randomised, placebo-controlled study (NCT02141035) in 20 patients with severe carpal tunnel syndrome, acetyl-L-carnitine did not improve nerve regeneration or functional recovery following surgery. In this study, patients were randomised to receive orally administered acetyl-L-carnitine at a dose of 3000 mg/day or placebo for 2 months after carpal tunnel release surgery. BCTQ scores and a set of physiological (i.e., motor and sensory conduction studies, static two-point discrimination, and pressure sensitivity) and clinical (i.e., hand dexterity) outcome measures were assessed at baseline and at 3, 6, and 12 months after the surgery. The extent of improvement was similar between experimental groups for all outcome measures analysed [55]. It should be stressed that in the research by Cruccu et al. [54], patients who had undergone carpal tunnel surgery were not eligible for taking part in the study. Moreover, the method of administration (initially parenteral followed by oral in [54] versus oral only in [55]) and length of treatment (4 months in [54] versus 2 months in [55]) were different. Therefore, the results of the two studies are not directly comparable and not necessarily discordant.

Diabetic Polyneuropathy

Diabetic neuropathy affects ~50% of patients with diabetes and is its devastating complication that contributes to morbidity and mortality or the disease. Diabetic neuropathy mainly comprises distal symmetric polyneuropathy, leading to sensory loss, pain, and motor dysfunction, and can result in diabetic foot ulcers requiring lower-limb amputations. To date, there is no treatment to effectively stop or reverse the progression of neuropathy [56].

In animal models, acetyl-L-carnitine improved several aspects of diabetic neuropathy [57–63]. Three studies assessed the effectiveness and safety of acetyl-L-carnitine in diabetic neuropathy [64–66] (Table 2). In the first clinical study, a multicentre, randomised, double-blind, placebo-controlled, parallel-group study by De Grandis et al. [64], treatment with acetyl-L-carnitine (500 mg twice daily intramuscularly for 10 days followed by 2000 mg daily administered orally for 355 days) resulted in improvement in neurophysiological parameters and pain reduction over a 1-year period [64]. The analysis of two randomised, placebo-controlled trials showed that acetyl-L-carnitine reduced pain and improved nerve regeneration and vibration perception in patients with diabetes treated with 500 or 1000 mg/day of the drug [66]. The efficacy and safety of acetyl-L-carnitine (500 mg three times a day) versus methylcobalamin (0.5 mg three times a day) to treat diabetic peripheral neuropathy was assessed in a Chinese multicentre, randomised, parallel-group, double-blind, double-dummy, positive-controlled, non-inferiority phase II clinical trial. After 24 weeks of treatment, significant reductions in neuropathy symptom and disability scores and in neurophysiological parameters were seen in both groups, with no difference between the two drugs safety-wise. The authors concluded that acetyl-L-carnitine and methylcobalamin had similar efficacy and safety in the treatment of diabetic polyneuropathy [65].

Aggregate analyses showed that acetyl-L-carnitine was more effective in patients with diabetic neuropathy than in patients with other peripheral neuropathies [67] and that acetyl-L-carnitine provided pain reduction of 20.2% (95% confidence interval [CI] 8.3%–32.1%, $p<0.0001$) with respect to baseline [68].

Chemotherapy-Induced Polyneuropathy

Chemotherapy-induced peripheral polyneuropathy affects up to 80% of patients treated and constitutes a series adverse event, the occurrence of which may require anti-cancer therapy dose adjustment [69]. The usefulness of acetyl-L-carnitine in polyneuropathy treatment and prevention was assessed by several studies [70–77] (Table 2). The two latest meta-analyses do not prove the hypothesis that acetyl-L-carnitine exerts a positive effect on chemotherapy-induced polyneuropathy [69, 77], and its use is not recommended by the ASCO guidelines [76].

Antiretroviral Toxic Neuropathy

Antiretroviral toxic neuropathy is the commonest human immunodeficiency virus (HIV)-associated distal symmetrical polyneuropathy caused by nucleoside analogue reverse transcriptase inhibitors used for the treatment of HIV [78]. Serum acetyl-L-carnitine levels are decreased in antiretroviral toxic neuropathy, prompting the hypothesis that its delivery could be a targeted treatment [79, 80]. Hart et al. designed a study to analyse the effect of long-term treatment with acetyl-L-carnitine on symptoms and cutaneous innervation and showed symptom improvement and peripheral nerve regeneration [80]. Later, the safety and efficacy of acetyl-L-carnitine in the symptomatic treatment of antiretroviral toxic neuropathy was analysed in a double-blind, parallel-group, placebo-controlled, multicentre trial of 90 patients. Compared to placebo, the treatment with intramuscular acetyl-L-carnitine significantly reduced weekly mean pain on the VAS, whilst during the open-label part of the study, oral acetyl-L-carnitine improved symptoms in the entire cohort, with no safety issues [81] (Table 2).

Fabry Disease

Fabry disease is a genetic disorder caused by a deficiency in lysosomal α-galactosidase A, of which neuropathic pain is the hallmark. Patients with Fabry disease experience peripheral neuropathy, sensory abnormalities, acute pain crises, and lifelong ongoing pain [82]. The peripheral neuropathy in Fabry disease is described as a small fibre neuropathy, meaning that small, unmyelinated nerve fibres are particularly affected [82].

In a mouse model of Fabry disease, acetyl-L-carnitine caused analgesia by up-regulating type-2 mGlu receptors. *GalA* gene knockout mice were treated with acetyl-L-carnitine for 30 days. Such treatment induced acute and long-lasting analgesia, which persisted for 1 month after drug withdrawal. Up-regulation of mGlu2 receptors was observed in cultured DRG neurons isolated from 30-day acetyl-L-carnitine-treated α-GalA knockout mice, which was no longer detectable in DRG neurons isolated 30 days after the end of treatment, hinting at an additional mechanism being responsible for the long-term analgesic effect [35].

Other Uses

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative condition characterised by loss of motor neurons, leading to limb weakness and/or weakness of bulbar muscles [83]. Pain is a common but rarely discussed symptom of ALS. Its prevalence is between 15% and 85% of patients with ALS [84]. Primary pain in ALS includes neuropathic pain and pain due to spasticity or cramps, whereas secondary pain is mainly nociceptive and may appear as muscle weakness and atrophy progress [83].

Given that acetyl-L-carnitine has a neuroprotective action shown in an animal model of ALS [85], it was hypothesised that treatment with acetyl-L-carnitine could help patients with ALS. The effects of acetyl-L-carnitine administered with riluzole compared to riluzole and placebo on disability and mortality were assessed in a cohort of 82 patients with definite/probable ALS [86]. A lower percentage of patients became self-insufficient in the acetyl-L-carnitine group than in the placebo group. The median survival was also longer in this acetyl-L-carnitine group (45 versus 22 months). The treatment was safe and well tolerated [86].

Additional data on the effects of acetyl-L-carnitine in patients with ALS were obtained in an observational, retrospective, multicentre, case–control study in Italy [87]. Forty-five patients were treated with 1.5 or 3 g/day of acetyl-L-carnitine given orally. An equal number of sex-, age-, site of onset-, disease-duration-matched untreated patients with ALS were analysed as a control group. Although the higher dose of acetyl-L-carnitine did not improve survival (adjusted odds ratio [aOR] 1.18, 95% CI 0.46–3.02), the lower dose did (aOR 0.27, 95% CI 0.10–0.71). For the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), a mean slope of −1.0 was observed in the treated group compared to −1.4 in the untreated

Table 2 Studies of acetyl-L-carnitine in patients with small fibre neuropathies

Type of study	Patient number	Cause of small fibre neuropathy	Acetyl-L-carnitine dosing, route of administration	Results
Diabetic neuropathy				
Randomised, double-blind, placebo-controlled, parallel-group multicentre study [64]	333	DM1/2	1000 mg/day or placebo IM, 10 days, followed by 2000 mg/day orally, 1 year	Improved neurophysiological parameters (significant improvement in nerve conduction velocity and amplitude compared to placebo [$p < 0.01$]) Significantly reduced pain on VAS at 12 months
Database analysis from two multicentre, randomised, double-blind, placebo-controlled studies [66]	1257	DM1/2	500 mg or 1000 mg/TID, 1 year	Significant improvements in sural and regenerating nerve fibre clusters No improvements in nerve conduction velocities and amplitudes Improved vibration perception Pain improvement in one study and in the combined cohort taking the dose of 1000 mg
Multicentre, randomised, parallel-group, double-blind, double-dummy, positive-controlled, non-inferior phase II clinical study [65]	232	DM1/2	Acetyl-L-carnitine at 500 mg/TID or methylcobalamin at 0.5 mg/TID, orally, 24 weeks	At week 24, significant reductions in both neuropathy symptom and neuropathy disability scores with no significant difference between groups
Chemotherapy-induced neuropathy				
Prospective case series* [70]	25	Paclitaxel, cisplatin	1 g/TID orally, 8 weeks	60% improvement in sensory neuropathy, 79% improvement in motor neuropathy

Table 2 continued

Type of study	Patient number	Cause of small fibre neuropathy	Acetyl-L-carnitine dosing, route of administration	Results
Pilot case series* [71]	42	Paclitaxel, cisplatin	1 g/day infusion over 1–2 h IV, ≥ 10 days (range: 10–20, median 14)	73% of patients ≥ 1 grade improvement in neuropathy severity
Multicentre, randomised, double-blind and placebo-controlled phase 2 study* [75]	239	Paclitaxel, cisplatin or vinblastine	1 g/TID or placebo orally, 8 weeks	Peripheral neuropathy improvement ≥ 1 at 8 weeks: 50.5% versus 24.1% ($p < 0.001$) Significant improvement in nerve electrophysiological examination and the Karnofsky performance score
Randomised, double-blind, placebo-controlled, phase 2 study** [72]	150	Sagopilone: 16 mg/m^2 every 3 weeks up to 6 cycles	1 g every 3 days or placebo, for the duration of chemotherapy	Significant reduction in high-grade neuropathy
24-week randomised, double-blind, placebo-controlled** [73]	409	Taxane	3 g/day or placebo, 24 weeks	No effect on neuropathy at 12 weeks; significant increase in neuropathy by week 24
Prospective randomised controlled pilot study** [101]	40	Paclitaxel	1 g/TID or placebo orally, 8 weeks	Reduced frequency of motor and sensory peripheral neuropathy, reduced side effects, improvement in NGF levels
Case–control study** [74]	32	Bortezomib, doxorubicin, dexamethasone, up to 8 cycles	3 g/BID or placebo, for the duration of chemotherapy	No effect on the incidence or severity of polyneuropathy
Antiretroviral toxic neuropathy				
Cohort study [80]	21	NRTI	1500 mg/BID orally, up to 33 months	Improved symptoms, peripheral nerve regeneration

Table 2 continued

Type of study	Patient number	Cause of small fibre neuropathy	Acetyl-L-carnitine dosing, route of administration	Results
Double-blind, parallel-group, placebo-controlled, multicentre study followed by open-label study [81]	90	NRTI	500 mg/BID or placebo IM, 14 days, followed by open-label dosing at 1000 mg/BID orally, 42 days	Significantly reduction in weekly mean pain ratings on VAS compared to placebo Symptom improvement during the open-label part of the study

BID, twice a day; DM1/2, type 1/2 diabetes mellitus; IM, intramuscular; IV, intravenous; NGF, nerve growth factor; NRTI, nucleoside reverse transcriptase inhibitors; TID, three times a day; VAS, visual analogue scale

*Treatment of chemotherapy-induced neuropathy

**Prevention of chemotherapy-induced neuropathy

patients ($p=0.0575$). No statistically significant difference was detected in forced vital capacity (FVC) or self-sufficiency. No safety issues emerged [87]. It is difficult to draw conclusions from the two studies, as their design and interventions differed. There is an ongoing phase 2/3 randomised, double-blind, placebo-controlled trial (NCT06126315) of the biological and clinical effects of acetyl-L-carnitine planning to recruit ~250 patients [88].

Besides the issue of its effectiveness, insight into the role of acetyl-L-carnitine in the pathophysiology of ALS was provided by Grossini et al. [19]. The researchers confirmed the fundamental role of oxidative stress and neurovascular unit in the pathogenesis of ALS. Treatment with acetyl-L-carnitine decreased the levels of markers of lipid peroxidation and increased the levels of antioxidants compared to healthy controls; however, the study did not include an untreated control group of patients with ALS [19]. A comprehensive review of the available evidence on the use of acetyl-L-carnitine in ALS was recently published [89].

Fibromyalgia affects up to 3% of the general population and is a syndrome characterised by widespread pain, fatigue, sleep disturbances, and cognitive dysfunction, somatic symptoms, and psychiatric disorders [90].

A preliminary randomised controlled trial to compare the effects of duloxetine and acetyl-L-carnitine on pain, depression, anxiety, and well-being in patients with fibromyalgia suggested that acetyl-L-carnitine was efficacious in improving depressive symptoms, pain, and quality of life [91]. A retrospective study analysed data on the use of acetyl-L-carnitine as an add-on treatment in 137 adult patients with fibromyalgia with pain lasting for over 3 months. The patients experienced a statistically significant improvement from baseline to the end of the observation in pain intensity on VAS (from 75.9 ± 1.56 to 51.9 ± 1.99; $p<0.001$). Patients without concomitant anti-fibromyalgia treatment achieved better pain reduction than patients who were on treatment at baseline. A total of 23 patients (16.7%) reported adverse events, including insomnia, shivering, headaches, and nausea; six patients discontinued due to adverse events [92].

Preclinical evidence suggests that acetyl-L-carnitine is endowed with antidepressive properties related to the epigenetic regulation of mGlu2 expression [32]. Persons affected by major depressive disorder manifested acetyl-L-carnitine deficiency compared to age- and sex-matched healthy individuals in two independent study centres. The degree of deficiency correlated with both the severity and age of onset of the disease [93]. A meta-nalysis showed that, compared with placebo/no intervention, the treatment with acetyl-L-carnitine significantly decreased the symptoms of depression, with fewer adverse events than those seen with established antidepressants [94]. However, to date, acetyl-L-carnitine is not indicated for the treatment of depression.

SAFETY

Although the studies included in this review identified no important safety issues, orally administered L-carnitine supplementation has been linked to a increase in trimethylamine (TMA) and trimethylamine-*N*-oxide (TMAO), as unabsorbed carnitine is metabolised by the gut microbiota to TMA and later oxidised to TMAO in the liver. Elevated serum levels of TMAO have been linked by some studies to an increased risk of cardiovascular disease [95]. The exact implications of these findings require more research. For this reason, Health Canada does not accede the use of L-carnitine and acetyl-L-carnitine in food supplements until additional information becomes available [96]. Considering the above, an effective way of avoiding the exposure of the gut microbiota to acetyl-L-carnitine is its parenteral administration. Intravenous or intramuscular delivery bypasses the intestinal lumen, preventing any interaction with microbial enzymes responsible for TMA formation. As a result, the biochemical pathway leading to TMAO is not activated.

DISCUSSION AND CONCLUSIONS

There is evidence for the usefulness of acetyl-L-carnitine in the prevention and treatment of a wide variety of neuropathy states. Admittedly, the available evidence is of variable quality, and it is hard to compare the studies because different experimental approaches, doses, administration schemes, and so on, have been applied. The effectiveness data available to date together with the basic biology studies most certainly warrant further research into this compound in the conditions discussed here and in clinical scenarios reviewed elsewhere [6].

The neuroprotective effect of acetyl-L-carnitine was documented in patients with peripheral neuropathies of different aetiologies [68]. Only one study examined the effectiveness and safety of acetyl-L-carnitine treatment in patients with multiple aetiologies including diabetic, alcoholic, traumatic, infective, and toxic origins [46]. The cohort was too small to analyse the effectiveness in subgroups of different aethiopathologies. The study showed that patients with mononeuropathies responded better than those with the involvement of multiple nerves. Mononeuropathies are more likely to be caused by a trauma or a localised infection, but this information is not present in the article [46]. More research is needed to understand whether acetyl-L-carnitine can help patients with the less studied aetiologies, such as infections or trauma.

Currently, only the Mayo Clinic guidelines on peripheral neuropathies recommend acetyl-L-carnitine amongst tier 1 agents [10]. By contrast, none of the mainstream guidelines, including those from the International Association for the Study of Pain (IASP; 2025 update), mention acetyl-L-carnitine as a therapeutic option alone or in combination with other agents [97]. IASP guidelines strongly recommend the use of α2δ-ligands (e.g., pregabalin), serotonin noradrenaline reuptake inhibitors, and tricyclic antidepressants. Scarzella's study demonstrated that combining acetyl-L-carnitine with pregabalin achieved greater effectiveness than either agent used independently [49]. While acknowledging that this was a relatively small retrospective study (n=81), the results suggest that in the

future, pending further evidence, acetyl-L-carnitine might be considered as an addition to first-line treatments currently recommended by IASP.

In addition to the aforementioned combination therapy including acetyl-L-carnitine and pregabalin, there are studies in which acetyl-L-carnitine was combined with other nutraceuticals [98–100]; however, the results available so far require independent corroboration.

Clearly, the conclusions of this review should be interpreted as hypothesis-generating rather than definitive, especially for indications with mixed evidence.

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Declarations

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