

# Acetyl-L-carnitine in painful peripheral neuropathy: a systematic review

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**Abstract:** Acetyl-L-carnitine (ALC) has shown a neuroprotective effect in patients with peripheral neuropathies of different etiologies. Preclinical studies demonstrated a central anti-nociceptive action, both in neuropathic and nociceptive pain models. The present review aims to provide the knowledge on the efficacy of ALC in patients with painful peripheral neuropathy, based on the evidence. Consistent with the PRISMA statement, authors searched PubMed, Embase and the Cochrane Database of Systematic Reviews for relevant papers, including those issued before April 2018. Two authors independently selected studies for inclusion and data extraction: only trials including patients with a diagnosis of peripheral neuropathy and involving at least 10 patients were considered for the purposes of this review. Fourteen clinical trials were revised, to provide the level of evidence for neuropathy. To assess the global efficacy of ALC in painful peripheral neuropathy, a meta-analysis of four randomized controlled trials was performed. Mean difference in pain reduction as measured on a 10-cm VAS, and 95% CIs were used for pooling continuous data from each trial. Four randomized controlled trials tested ALC in patients with neuropathy secondary to diabetes and to antiretroviral therapy for HIV. Compared to placebo, ALC produced a significant pain reduction equal to 20.2% (95% CI: 8.3%-32.1%,  $P<0.0001$ ) with respect to baseline. Clinical trials also showed beneficial effects on nerve conduction parameters and nerve fiber regeneration, with a good safety profile. These data indicate that ALC provides an effective and safe treatment in patients with painful peripheral neuropathy. We recommend further studies to assess the optimal dose and duration of the therapeutic effect (also after treatment withdrawal).

**Keywords:** neuropathic pain, treatment, neuroprotective function, epigenetic mechanism

## Introduction

An improved understanding of the pathophysiologic mechanism of neuropathic pain has led to the use of previously unexplored therapies, with encouraging results: among them, the acetyl-L-carnitine (ALC), ie the acetyl ester of L-carnitine produced by the human brain, liver and kidney, represents one of such recent therapeutic approaches. This molecule is an acetyl-group donor and plays an important role on mitochondrial energy homeostasis and detoxification<sup>1,2</sup> Besides strengthening the actions of Nerve Growth Factor (NGF) actions,<sup>3-5</sup> and promoting peripheral nerve regeneration,<sup>6,7</sup> ALC revealed a neuroprotective function in vitro,<sup>2,8</sup> in vivo<sup>9</sup> and in animal models of diabetic neuropathy.<sup>10</sup> ALC has antiapoptotic effects in peripheral mononeuropathy models,<sup>11</sup> an antioxidant activity<sup>12</sup> and accretes acetylcholine production. Microdialysis studies have shown an increased acetylcholine release in both rat striatum and hippocampus following ALC administration.<sup>13</sup>

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Due to its analgesic effect, ALC has gained a growing clinical interest in different forms of chronic-pain neuropathy, not only for treatment, but also for pain prevention.<sup>14,15</sup> Several experimental models of neuropathic pain documented the antinociceptive effect of ALC; such model encompassed streptozotocin- and chemotherapy-induced neuropathy, as well as the sciatic nerve chronic constriction injury.<sup>6,16</sup> Moreover, ALC provides a significant antinociceptive effect even after the development of neuropathic pain. These analgesic properties result from different mechanisms. ALC is the only drug whose analgesic effect is due to an epigenetic mechanism, based on the acetylation of p65/RelA, a transcription factor belonging to the NFkB family. Acetylation of p65/RelA leads to a strengthened expression of type-2 metabotropic glutamate (mGlu2) receptors in the dorsal root ganglia and dorsal horns of the spinal cord, thus reducing the glutamate release from primary afferent sensory fibers.<sup>17,18</sup> The analgesic effect induced by ALC persisted for at least 14 days after drug interruption. A long-term analgesic effect was also observed in mice after chronic constriction injury of the sciatic nerve.<sup>17</sup>

The effect on pain of ALC is also modulated by nicotinic and muscarinic antagonists, as shown in a number of animal studies, thus suggesting the role of the cholinergic pathway in the antinociceptive activity of this drug.<sup>19,20</sup>

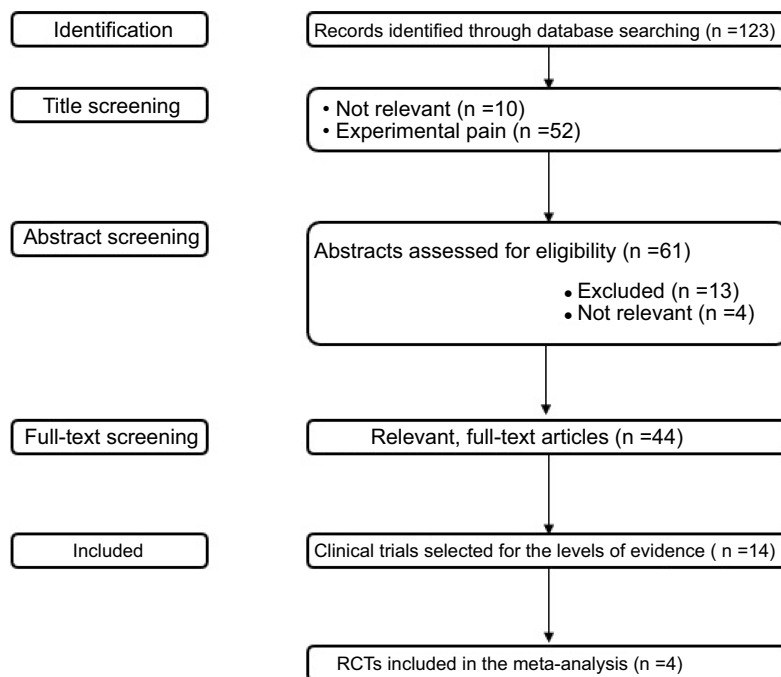
ALC may raise the uptake of acetyl-CoA into the mitochondria and, due to its similarity in structure to acetylcholine, it may also produce cholinomimetic effects.<sup>21</sup>

This systematic review and meta-analysis aim to provide the actual knowledge, based on the evidence, of ALC efficacy compared to placebo in the treatment of neuropathic pain in patients with peripheral neuropathy.

## Materials and methods

### Search process

We searched PubMed, Embase and the Cochrane Database of Systematic Reviews for relevant papers, considering publications issued before April 2018. The following search terms were used: “acetyl-L-carnitine”, “neuropathic pain”, and “neuropathy”. Full-length, original communications were included, limiting the search to English-language publications. The review process was carried out by two reviewers: only publications independently approved by the two authors were taken into account (Figure 1). The following inclusion criteria were considered: trials including patients with a diagnosis of neuropathic pain related to peripheral neuropathy, and a minimum sample size of 10 patients. A revision of the selected clinical trials was carried out, to provide the level of evidence, according to the guidelines for clinical practice recommendations of the American Academy of



**Figure 1** Flowchart of the search process.

**Abbreviation:** RCTs, randomized controlled trial.

Neurology (AAN).<sup>22</sup> A meta-analysis of randomized control trials (RCTs), testing the effect of ALC in patients with painful peripheral neuropathy was also performed. For the purposes of the meta-analysis, we considered only the RCTs with a homogeneous measure of the ALC effect on pain, compared to placebo. The risk of bias of the included RCTs was evaluated independently by two reviewers, in accordance with the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.

## Statistical analysis

We pooled the mean reduction of pain, compared to placebo, as measured on a 10-cm VAS. The pooled effect of each study was described in terms of mean difference (MD) with 95% CIs. Heterogeneity among studies was assessed by analysing the relevant forest plots; the statistical analysis consisted of a  $\chi^2$  test of homogeneity and the evaluation of the inconsistency index  $I^2$ .<sup>23</sup> An inconsistency index  $I^2 > 50\%$  indicated a statistically significant among-study heterogeneity: in this case, studies were pooled using random-effects model. A subgroup analysis, based on the cause of neuropathy (diabetes and antiretroviral toxic neuropathy), was carried out; heterogeneity between groups was also evaluated. Forest plots of the individual studies and the pooled average were also computed, with the aid of GraphPad Prism 7.0.

## Results

### Clinical trials overview

Out of 44 full-text articles, the search process led to the selection of fourteen clinical trials, whose characteristics are summarized in Table 1. Such trials encompassed both RCTs and open-label studies. To each of these studies we assigned a classification level according to the AAN method.<sup>22</sup> Among them, only four RCTs were considered for the meta-analysis.

### Acetyl-L-carnitine in diabetic neuropathy

Three Class II RCTs compared ALC versus placebo in a total of 1590 patients with diabetic peripheral neuropathy.<sup>24,25</sup> The treatment efficacy on pain was evaluated using a VAS.

Sima and colleagues carried out two RCTs with the same design. ALC was administered at two doses (500 or 1,000 mg) three times a day (t.i.d.) for 1 year. Patients treated with 1,000 mg ALC t.i.d. showed significant

improvements at both 26 and 52 weeks. Type 2 diabetes, adequate drug compliance, and HbA1c  $> 8.5\%$  were associated to the greatest benefit in pain reduction. Pain relief was linked to improvements in clinical symptom scores and morphometric parameters of sural nerve biopsy, ie the increased fiber numbers and clusters of regenerating fibers. No significant differences in nerve conduction study data and in the incidence of adverse events between the two groups of patients were observed.<sup>24</sup>

In the RCT of De Grandis and colleagues, 1,000 mg/day of ALC were administered intramuscularly for 10 days; the dosage was then raised to 2,000 mg/day, administered orally, until the end of the study (355 days).<sup>25</sup> After 12 months of treatment, a significant reduction in the mean VAS scores for pain was observed in patients treated with ALC, compared with the placebo group. A significant improvement in nerve conduction study parameters was also found in treated patients. No serious adverse events were reported.

A multicenter, double-blind RCT assessed the efficacy and safety of ALC in diabetic peripheral neuropathy compared with methylcobalamin.<sup>26</sup> The study encompassed 232 patients, randomized to receive oral ALC 500 mg t.i.d. or methylcobalamin 0.5 mg t.i.d. for 24 weeks. At the end of the treatment period, patients from both groups showed significant reductions in both the neuropathy symptom score and neuropathy disability score, with no meaningful difference between the two groups. Neurophysiological parameters were also improved in both groups.

### Acetyl-L-carnitine in antiretroviral toxic neuropathy

One Class II RCT was conducted in patients with antiretroviral toxic neuropathy.<sup>27</sup> This is a double-blind placebo-controlled study testing the safety and efficacy of ALC compared to placebo in the treatment of pain in HIV-positive patients with distal symmetric polyneuropathy related to antiretroviral drugs.<sup>28</sup> Ninety patients were included in the trial, randomized to receive ALC 1,000 mg/day (500 mg intramuscularly twice daily) during the 14-day double-blind phase. During the 42 days of open-treatment follow-up phase, ALC was administered in the form of 1,000 mg oral sachets twice a day. The treatment efficacy on pain was evaluated using VAS, Total Symptom Score (TSS), Clinical Global Impression of Change, McGill Pain Questionnaire (MPQ), and the need

**Table 1** Clinical trial in patients with peripheral neuropathy

Author/year	Study type	Neuropathy	Sample Size	Study duration (months)	ALC daily dose (mg)	Outcome Measures	Findings	Class
Sima et al United States, Canadian study (UC), 2005 Sima et al United States, Canadian and European study (UCE), 2005	RCT	Diabetic peripheral neuropathy	1257	13	500 or 1000	VAS scale, NCS	VAS reduction: $-25.53 \pm 28.75$ mm VAS reduction: $-21.75 \pm 34.58$ mm	II
De Grandis et al, 2002	RCT	Diabetic peripheral neuropathy	333	12	2000	VAS scale, NCS	VAS reduction: $-39\%$ compared to baseline NCS improvement: $+5.7$ m/sec compared to baseline	II
Sheyu et al, 2016	RCT	Diabetic peripheral neuropathy	232	6	500	NCS and neuropathy symptom score	NCS improvement: $5.03 \pm 10.78$ m/sec NCS improvement: $4.01 \pm 3.25$	II
Youle et al, 2007	RCT	Antiretroviral toxic neuropathy	90	0.5	1000	VAS scale	VAS reduction: $-0.89 \pm 0.75$ mm	II
Hart et al, 2004	Open-label uncontrolled trial	Antiretroviral toxic neuropathy	21	33	3000	Skin innervation	Epidermal, dermal and sweat gland innervation reached 92%, 80% and 69%, respectively, after 6-month treatment	IV
Valcour et al, 2009	Open-label uncontrolled study	Antiretroviral toxic neuropathy	21	6	3000	GPIS, skin innervation, mtDNA copies/cell	GPIS improvement: $-0.079$ compared to baseline No changes in skin innervation and mtDNA copies/cell	IV
Osio et al, 2006	Open-label uncontrolled study	Antiretroviral toxic neuropathy	20	1	2000	Short-form McGill Pain Questionnaire	Pain reduction: $-21\%$ compared to baseline	IV
Scarpini et al, 1997	Open-label uncontrolled study	Antiretroviral toxic neuropathy	16	0.75	500 or 1000	Huskisson's analogic scale	Pain reduction in 62.5% of subjects	IV
Sun et al, 2016	RCT	Chemotherapy induced neuropathy	239	2	3000	Peripheral neuropathy grade (NCI-CTC), NCS	Reduced neurotoxicity: 50.5% of patients NCV improvement: 60.7% of patients	II

(Continued)

Table 1 (Continued).

Author/year	Study type	Neuropathy	Sample Size	Study duration (months)	ALC daily dose (mg)	Outcome Measures	Findings	Class
Maestri et al, 2005	Open-label uncontrolled study	Chemotherapy induced neuropathy	27	0.25	1000	Peripheral neuropathy grade (WHO)	At least one WHO grade improvement in 73% of patients	IV
Bianchi et al, 2005	Open-label uncontrolled study	Chemotherapy induced neuropathy	25	2	3000	Total neuropathy score	TNS improvement: 92% of patients	IV
Cruccu et al, 2018	Open-label uncontrolled study	Carpal tunnel syndrome	82	4	1000	NCS, BCTQ, NPSI	SCV changed from 34.7±5.6 m/s at t0 to 36.7±6.6 m/s at t120 Symptom and functional BCTQ decrease: -39% and 18% compared to baseline NPSI decrease: -38% to -56% compared to baseline	IV
De Grandis et al, 1995	RCT	Peripheral neuropathy of different etiologies	426	1	2000	NCS	NCV improvement in patients with mononeuropathies and in sensory nerve neuropathies, compared to placebo	II

**Abbreviations:** ALC, acetyl-L-carnitine; RCT, randomized controlled trial; NCS, nerve conduction study; NSS, neuropathy symptom score; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; GPS, gracely pain intensity scale; NCV, nerve conduction velocity; TNS, total neuropathy score; SCV, sensory conduction velocity; BCTQ, Boston Carpal tunnel questionnaire; NPSI, neuropathic pain symptom inventory.

Table 2 Meta-analysis in patients with diabetic and antiretroviral toxic neuropathy

Study	ALC				Placebo			
	Baseline	Reduction	Reduction %	N	Baseline	Reduction	Reduction %	N
De Grandis, 2002	–	–1.93±2.09	–39.4±42.7	95	–	–0.35±1.10	–7.7±24.2	104
Sima UC, 2005	5.99±2.41	–2.55±2.87	–42.6±48.0	70	5.04±2.19	–0.97±3.11	–19.3±61.7	48
Sima UCE, 2005	5.69±2.69	–2.17±3.46	–38.2±60.8	58	5.32±2.60	–1.45±2.75	–27.3±51.7	61
Youle, 2007	6.16±2.26	–1.32±1.84	–21.4±29.9	43	6.17±1.81	–0.61±1.55	–9.9±25.1	44
<b>Pooled analysis</b>				<b>266</b>				<b>257</b>
								<b>MD % (95% CI)</b>
								–31.7 (–41.5; –21.9)
								–23.3 (–44.1; –2.5)
								–11.0 (–31.3; 9.4)
								–11.5 (–23.2; 0.1)
								<b>–20.2 (–32.1; –8.3)</b>

Notes: Test for heterogeneity:  $\tau^2=88.58$ ;  $\chi^2=8.06$ ,  $d/3$  ( $p=0.05$ );  $I^2=62.8\%$ . Test for overall effect:  $Z=3.32$  ( $p<0.0001$ ). Results are expressed as mean  $\pm$  SD. Heterogeneity indexes:  $\tau^2$ ,  $\chi^2$ ,  $I^2$ .  
Abbreviation: ALC, acetyl-L-carnitine.

for rescue analgesics. For the efficacy-evaluable population, the group of patients treated with ALC showed a significantly greater reduction in pain, compared to the placebo group. During the open-label phase, VAS, TSS and MPQ revealed a pain relief. Intramuscular and oral treatments were generally safe and well tolerated; the viral load, CD4/CD8 ratio and CD4 and CD8 counts remained stable, thus revealing that ALC treatment was not associated with any progression of HIV infection.

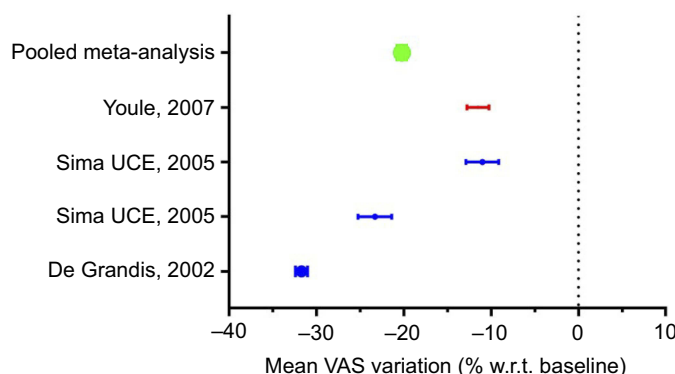
Several open-label studies including patients with anti-retroviral toxic neuropathy have been carried out. One study, involving 21 HIV-positive patients with established neuropathy, assessed the effect of oral ALC (1,500 mg twice daily) on dermal and intraepidermal innervation.<sup>29</sup> After a 6-month treatment, the mean immunostaining area for small sensory fiber increased in all fiber types, including sympathetic fibers: the epidermal, dermal and sweat gland innervation reached 92%, 80% and 69%, respectively compared with the control group. Neuropathic pain grade improved in 76% of patients, whereas it remained unchanged in 19%. No association of ALC treatment with any progression of HIV infection was observed. An open-label, single-arm pilot study involving 21 patients, evaluated the effect of 3,000 mg ALC daily on the intra-epidermal nerve fiber (IENF) density and mitochondrial DNA (mtDNA) copies/cell.<sup>30</sup> Whereas IENF density and mtDNA copies/cell did not change after therapy, improvements in neuropathic pain, paresthesias, and symptoms of numbness were observed. An open-label study, involving 20 subjects with painful antiretroviral toxic neuropathy, tested the efficacy of oral ALC at a dose of 2,000 mg/day for a 4-week period.<sup>31</sup> Mean pain intensity score, evaluated using the modified short-form MPQ, was significantly lowered during the study, whereas electrophysiological parameters did not show significant changes. Other two open label studies, totaling 26 patients, revealed a positive effect of ALC in reducing neuropathic pain intensity.<sup>32,33</sup>

Acetyl-L-carnitine in chemotherapy induced neuropathy

Clinical studies tested the neuroprotective effect of ALC in chemotherapy-induced neuropathy but no data about neuropathic pain reduction are available.

A prospective, double-blind, Class II RCT study totaling 239 patients with chemotherapy-induced peripheral neuropathy tested the effect of oral administration of





**Figure 2** Forest plot of randomized controlled trials in the meta-analysis. Each value is expressed as mean difference (95% CI).

ALC 3 g/day.<sup>34</sup> This study considered as primary endpoint the improvement of peripheral neuropathy by at least one grade according to the National Cancer Institute Common Toxicity Criteria version 3.0. Patients conditions were assessed at week 4, 8 and 12 after enrollment. At week 8, 51.6% patients treated with ALC met the primary endpoint, compared with 23.1% of patients in the placebo group. Secondary endpoints, such as sural nerve conduction velocity and the Karnofsky physical score showed also a significant improvement in patients treated with ALC, compared to the placebo group. No significant difference in the incidence of adverse events between the two groups was observed.

Two open label studies tested the effect of ALC in patients with neuropathy induced by paclitaxel and cisplatin.<sup>35,36</sup> Maestri and colleagues tested the effect of ALC 1 g/day i.v. infusion over 1–2 h for at least 10 days in 27 patients; the peripheral neuropathy improved in 73% of them. Bianchi and colleagues tested oral ALC (1 g t.i.d.) for 8 weeks in 25 patients. The total neuropathy score, including neurophysiological measures, improved in 92% of them.

Three studies totaling 578 patients with cancer investigated the effect of ALC in preventing chemotherapy-induced neuropathy, but no positive effect was detected.<sup>37–39</sup>

## Acetyl-L-carnitine in patients with carpal tunnel syndrome

Neuropathic pain is a common symptom in patients with Carpal tunnel syndrome (CTS).<sup>40</sup>

A recent multicenter, examiner-blinded, clinical and neurophysiological study assessed the efficacy of ALC on neuroprotection, pain, and function in CTS.<sup>15</sup> The

study included eighty-two patients with CTS of mild-to-moderate severity. Patients conditions were assessed at baseline and after 10, 60 and 120 days of treatment. After a first 10-day period of intramuscular injections ALC 500 mg b.i.d., patients received an oral treatment consisting of one tablet of ALC 500 mg b.i.d., for 110 days. Each patient underwent a median nerve conduction study, the Boston Carpal Tunnel Questionnaire (BCTQ) and the Neuropathic Pain Symptom Inventory (NPSI). The BCTQ score was significantly improved, especially in the symptom component. Squeezing, pressure pain and pain evoked by pressure, were significantly lowered. These symptom improvements were detected after the first 10 days of intramuscular treatment and persisted throughout the 4-month treatment period. All sensory neurophysiological measures significantly improved.

## Meta-analysis of RCTs in diabetic and HIV-related painful peripheral neuropathy

Four RCTs tested the effect of ALC in comparison with placebo in patients with diabetic and antiretroviral toxic neuropathy (Table 2). A random-effects model was used for the analysis, given that the heterogeneity indexes approached the statistical significance ( $\tau^2=88.58$ ;  $\chi^2=8.06$ ,  $df=3$ ,  $P=0.045$ ;  $I^2=62.8\%$ ). Compared to placebo, ALC produced a pain reduction equal to 20.2% (95% CI: 8.3–32.1%,  $P<0.0001$ ) with respect to baseline. The forest plot, displaying the results from individual studies as well as the pooled effect with the relevant CI, is reported in Figure 2. A subgroup analysis considering only the three studies conducted in diabetic peripheral neuropathy was carried out (Table 3). Even in this case, a random-effects model was used ( $\tau^2=50.28$ ;  $\chi^2=3.40$ ,  $df=2$ ,  $P=0.18$ ;  $I^2=41.2\%$ ). With respect to baseline, the mean difference in pain

**Table 3** Subgroup analysis in patients with diabetic peripheral neuropathy

Subgroup (diabetes)	ALC			Placebo			MD % (95% CI)
	Baseline	Reduction	Reduction %	Baseline	Reduction	Reduction %	
De Grandis, 2002	–	–1.93±2.09	–39.4±42.7	–	–0.35±1.10	–7.7±24.2	–31.7 (–41.5; –21.9)
Sima UC, 2005	5.99±2.41	–2.55±2.87	–42.6±48.0	5.04±2.19	–0.97±3.11	–19.3±61.7	–23.3 (–44.1; –2.5)
Sima UCE, 2005	5.69±2.69	–2.17±3.46	–38.2±60.8	5.32±2.60	–1.45±2.75	–27.3±51.7	–11.0 (–31.3; 9.4)
<b>Pooled analysis</b>							<b>–24.6 (–36.8; –12.4)</b>

**Notes:** Test for heterogeneity:  $\chi^2=50.28$ ;  $\chi^2=3.40$ ,  $df=2$  ( $P=0.18$ );  $I^2=41.2\%$ . Test for overall effect:  $Z=3.95$  ( $P<0.0001$ ). Test for subgroup differences:  $\chi^2=2.31$ ,  $df=1$  ( $P=0.13$ );  $I^2=56.7\%$ . Results are expressed as mean  $\pm$  SD. Heterogeneity indexes:  $\chi^2$ ,  $\tau^2$ ,  $I^2$ .

**Abbreviation:** ALC, acetyl-L-carnitine.

reduction was equal to 24.6% (95% CI: 12.4%–36.8%,  $P<0.0001$ ): these results match those reported by Li and colleagues.<sup>14</sup> The test addressing the differences between the diabetic subgroup versus the HIV therapy-related study revealed a meaningful heterogeneity ( $\chi^2=2.31$ ,  $df=1$ ,  $P=0.13$ ;  $I^2=56.7\%$ ). Table 4 provides details on the risk of bias assessment for each study. In general, reporting of randomization methods and treatment allocation was clearly stated in De Grandis and colleagues<sup>25</sup> and in Youle and colleagues<sup>28</sup> whereas it was uncertain in Sima and colleagues<sup>24</sup> therefore associated with an uncertain bias risk. Allocation concealment and blinding were addressed in De Grandis and colleagues.<sup>25</sup>

### Effects of ALC on nerve function

Controlled trials in large cohorts of patients with peripheral neuropathy of different etiologies tested the effect of ALC on neurophysiological measures. In the double-blind RCT of De Grandis and colleagues, involving 333 patients with diabetic neuropathy, the mean nerve conduction velocity and amplitude significantly improved, in comparison with placebo.<sup>25</sup> In two randomized placebo-controlled trials, totaling 1257 patients with diabetic neuropathy, Sima and colleagues failed to find any significant electrophysiological change in patients treated with 500 or 1,000 mg ALC, although a significant improvement in the vibration perception threshold was reported.<sup>24</sup> A short-term, double-blind clinical study involving 426 patients with peripheral neuropathy of different etiologies, showed statistically meaningful differences between the ALC and placebo groups in terms of mean conduction velocity improvement.<sup>41</sup>

A double-blind, randomized placebo-controlled study, totaling 239 patients with chemotherapy-induced peripheral neuropathy, reported a meaningful increase of sural nerve conduction velocity after ALC treatment.<sup>34</sup>

The neuroprotective effect of ALC in CTS was tested in a multicenter, examiner-blinded, clinical and neurophysiological study totaling 82 patients. The primary outcome, ie the sensory conduction velocity of the median nerve, significantly improved after 4 months of treatment. Such an improvement, detected after the first 60 days of treatment, persisted throughout the treatment period, lasting 4 months. The sensory action potentials amplitude of the median nerve increased from baseline to the end of the study.<sup>15</sup> In addition, both the symptom and functional BCTQ scores significantly decreased.



**Table 4** Bias assessment

Methodological items	De Grandis, 2002	Sima UC, 2005	Sima UCE, 2005	Youle, 2007
Random sequence generation	Low risk	Uncertain risk	Uncertain risk	Low risk
Allocation concealment	Low risk	Uncertain risk	Uncertain risk	Uncertain risk
Blinding of participants and personnel	Low risk	Uncertain risk	Uncertain risk	Uncertain risk
Blinding of outcome assessment	Low risk	Uncertain risk	Uncertain risk	Uncertain risk
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk
Selective reporting	Uncertain	Uncertain risk	Uncertain risk	Uncertain risk
Other bias	Low risk	Low risk	Low risk	Low risk

## Discussion

According to preclinical and clinical studies, ALC can be considered both an etiological and symptomatic treatment in patients with peripheral neuropathy, with a good safety profile. ALC operates via several mechanisms, inducing regeneration of injured nerve fibers, reducing oxidative stress, promoting DNA synthesis in mitochondria, and increasing NGF concentrations in neurons, thus promoting neurite extension.<sup>3,7</sup> A lack of carnitine reduces energy synthesis by impairing fatty acid degradation: this condition was reported in association with diabetes and its complications.<sup>42,43</sup> A cross-sectional study in HIV patients treated with antiretroviral nucleoside analogs showed that in patients with axonal peripheral neuropathy ALC levels are significantly lower compared to the control groups.<sup>44</sup> Under specific conditions, the demand for ALC may exceed the capacity to synthesize this essential micronutrient.<sup>25</sup> In addition, ALC production may be impaired by genetic defects.

ALC showed analgesic properties, by relieving acute and in chronic pain. Several clinical studies reported an improvement in symptoms after ALC supplementation in patients with peripheral neuropathy of different etiologies.<sup>31,36,45</sup> Several works, describing different neuropathic pain models, confirmed the antinociceptive effect of ALC. Such an effect results from different mechanisms, including the activation of muscarinic cholinergic receptors, and the increased expression of mGlu2 receptors in dorsal root ganglia neurons, by means of an acetylation mechanism involving transcription factors of the nuclear factor (NF)-kappaB family.<sup>17,20</sup> Noteworthy, the analgesic effect of ALC exceeds by several days or weeks the end of treatment, in models of chronic inflammatory and neuropathic pain. This enforces the role of ALC as an analgesic drug and supports the role of the epigenetic mechanisms in the treatment of chronic pain.<sup>17</sup>

For the first, a systematic review of literature was carried out, by providing a classification for the available clinical trials, and the level of evidence for: diabetic neuropathy, antiretroviral toxic neuropathy, chemotherapy induced neuropathy and CTS.

According to the AAN classification, ALC is probably effective in diabetic neuropathy. The presence of a single Class II trial for each type confirm the possible effect of ALC in both antiretroviral toxic neuropathy and in chemotherapy induced neuropathy. No RCT was performed in patients with CTS, but results obtained from a recent multicenter, examiner-blinded, clinical and neurophysiological study are promising.

Pooled results from the present meta-analysis, including four RCTs in patients with diabetic and antiretroviral toxic neuropathy, showed the efficacy of ALC compared to placebo in reducing pain intensity. In the subgroup analysis, patients with diabetic neuropathy reported greater pain reduction compared to patients with HIV-related peripheral neuropathy. Moderate heterogeneity, as measured by the  $I^2$  index, was observed among the RCTs; no significant heterogeneity was found in studies belonging to the diabetes subgroup. This meta-analysis has some limitations: only four RCTs with small or moderate sized were included. The length of follow-up was relatively short- and the long-term impact of ALC is unknown.

According to a recent systematic review and meta-analysis the effect of ALC on VAS in patients with painful neuropathy was similar for different administration routes (intramuscular and oral sequential administration and oral administration only).<sup>14</sup>

A recent multicenter, examiner-blinded, clinical and neurophysiological study assessed the effects of ALC in patients with mild to moderate CTS.<sup>15</sup> By means of its neuroprotective action and central anti-nociceptive properties, ALC provided a significant pain reduction, as measured by NPSI questionnaire. More in detail, squeezing pain, pressure pain and pain evoked

by pressure, were significantly lowered. Pain reduction was detected after the first 10 days of intramuscular treatment. The intramuscular administration could allow reaching high concentrations of ALC in the central nervous system, an essential condition for activating and boosting the epigenetic mechanisms underlying the analgesic action of the drug. However, once the epigenetic mechanism has been triggered, no more differences between intramuscular and oral administration are expected.

Future RCT trials in patients with painful peripheral neuropathy of different etiology are needed.

## Conclusion

ALC is an effective and safe treatment in painful peripheral neuropathy, especially in diabetic patients. Future studies aiming to assess the duration of the therapeutic efficacy and the optimal dose in larger populations, possibly with longer follow-up periods, are required.

The pain reduction induced by ALC may be mediated by both a neuroprotective and a central anti-nociceptive mechanism. Future studies should investigate the role of the two mechanisms.

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