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Safety and efficacy of alpha-lipoic acid oral supplementation in the reduction of pain with unknown etiology: A monocentric, randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Introduction: Extensive evidence suggests that alpha-lipoic acid (ALA) is effective in diabetic neuropathy pain management. However, little is known on its safety and efficacy in reducing idiopathic pain in normoglycemic subjects. The aim of this study was to evaluate ALA food supplement safety and efficacy in the reduction of different forms of idiopathic pain.

Methods: Two-hundred and ten normoglycemic adults suffering from idiopathic pain (i.e. 57 subjects with primitive neuropathic pain, 141 subjects with arthralgia with unknown etiology, and 12 subjects with idiopathic myalgia) were randomized to receive placebo, 400 mg/day, or 800 mg/day of ALA. Participants underwent two visits (at baseline = t0, and after 2 months = t1) in which two validated questionaries for pain (numerical rating scale [NRS] and visual analogue scale [VAS]) were collected; fasting blood glucose assessment, adverse effects, and renal and hepatic toxicity were also monitored.

Results: At t1, none of subjects treated with ALA reported a decreased glycemia or adverse effects. The treated subjects showed a significant reduction in NRS ($p < 0.001$) while the placebo group did not show any NRS reduction ($p = 0.86$). Similar results were also obtained for VAS. Statistical analysis aimed at detecting possible differences in NRS and VAS scores among treatment groups based on the source of pain did not reveal any significant effect.

Conclusions: Since the management of idiopathic pain is challenging for physicians, the use of ALA food supplements could be a feasible option, based on its safety and efficacy compared to commonly-used analgesic drugs.

Abbreviations: ALA, Alpha-lipoic acid; AMPK, AMP-activated protein kinase; ARs, Adverse reactions; BMI, Body mass index; CRE, Creatinine; CRF, Case report form; DHLA, dihydrolipoic acid; EFSA, European Food Safety Authority; GLUT4, Glucose transporters; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IAA, Insulin autoantibodies; IAS, Insulin autoimmune syndrome; IASP, International Association for the Study of Pain; ICD, International Statistical Classification of Diseases and Related Health problems; IPS, Italian Phytovigilance System; IR, Insulin receptor; IRS-1, Insulin receptor substrate-1; LMM, Linear Mixed Model; NDA, Panel on Nutrition, Novel Foods and Food Allergens; NRS, Numerical rating scale; NSAID, Non-steroidal anti-inflammatory drug; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SNRIs, Serotonin–norepinephrine reuptake inhibitors; VAS, Visual analogue scale; WHO, World Health Organisation.

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1. Introduction

Alpha-lipoic acid (1,2-dithiolane-3-pentanoic acid, ALA), also known as thioctic acid, is an endogenous substance produced at the mitochondrial level from octanoic acid and cysteine, naturally occurring in many common animal and plant foods and used as a food supplement ingredient for at least three decades [1]. ALA is involved in various metabolic pathways as a cofactor for several enzymes, in the antioxidant defense system, where it is able to regenerate other essential antioxidant molecules through its reduced form (dihydrolipoic acid), acts as a chelating agent for heavy metals, and repairs proteins, lipids, and DNA damaged by oxidative reactions [2–5].

Various biological properties have been ascribed to ALA over the last two decades, mainly due to its antioxidant and anti-inflammatory activities [6]. As growing evidence suggests a role for reactive oxygen species and antioxidants in pain modulation, [7–10] several clinical trials have highlighted the beneficial effects of ALA in subjects suffering from different kinds of acute and chronic pain [11]. The International Association for the Study of Pain (IASP) defines pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*" [12], thus suggesting the need to always consider pain as an important symptom for diagnosis as well as a crucial therapeutic target. In this context, the treatment of pain with ALA food supplements has recently been the subject of research interest, which has produced a robust body of evidence regarding its safety and efficacy as reported below. The use of ALA food supplements represents an interesting option, especially in primary pain with unknown etiology where no specifically-targeted drug can be selected, and where symptomatic drugs may not always be effective but may be associated with serious adverse effects under prolonged treatment. Recently, several clinical trials have found significant improvements in pain following ALA oral supplementation, at doses ranging from 400 to 600 mg/day, on pain in conditions such as migraine, back pain, carpal tunnel syndrome pain, and burning mouth syndrome pain [13–16]. Opposing conclusions were reached by two other clinical trials, in which the efficacy of ALA was tested against chemotherapy-induced peripheral neuropathy and fibromyalgia, although these studies suffered several limitations (i.e. small size of the trial, poor patient compliance) [17,18].

As far as the safety of ALA is concerned, a number of clinical trials report that ALA is very well tolerated and no significant adverse effects have been observed versus placebo [1, 17–24]. ALA safety was also demonstrated in pregnant women and their newborns by an observational retrospective study carried out on 610 expectant women treated for 7 days with a dose of 600 mg/day [11]. Another study, carried out in older subjects (15 subjects, age $\geq$ 65 years), demonstrated the safety of ALA at a dose of 600 mg/mL, but found that this compound was not completely tolerated. At a dose of 1200 mg/day, ALA induced gastrointestinal side effects and flushing sensations which were reduced with gastrointestinal prophylaxis, thus improving ALA tolerability [25]. Aside from these light and expected side effects of oral supplementation, ALA can trigger the development of insulin autoimmune syndrome (IAS), also called Hirata's disease, in predisposed individuals. This condition is strongly associated with alleles DRB1 * 04:06, DRB1 * 04:03 and DRB1 * 04:07, which are extremely rarely observed in the European population, but are more common in Asian populations. IAS is a rare condition characterized by hypoglycemic episodes due to the presence of high titers of insulin autoantibodies (IAA). The complex derived from the interaction between insulin and insulin autoantibodies interferes with the bonding of insulin to its receptor, leading to an increase in unbound insulin concentrations and resulting in hypoglycemic episodes [26]. IAS causes neuroglycopenic, neurogenic and cholinergic symptoms [27,28]. IAS usually resolves itself within a few months once the trigger is removed, although some patients require pharmacological treatment.

Many clinical trials on the efficacy of ALA are focused on the reduction of diabetic polyneuropathy symptoms in diabetic patients, and extensive evidence suggests that ALA decreases glucose levels. ALA plays a role in insulin modulation, and ameliorates insulin resistance through different mechanisms of action (i.e. increase of sugar uptake by the redistribution of glucose transporters as GLUT4) to the plasma membrane, increase in the abundance and intrinsic activity of GLUT4, phosphorylation of the insulin receptor (IR) and insulin receptor substrate-1 (IRS-1), and activation of intracellular AMP-activated protein kinase (AMPK) [29]. Nevertheless, studies evaluating the effects of ALA on glycemia in normoglycemic or prediabetic subjects are limited [13, 32–33].

Considering the efficacy of ALA food supplements on pain, and the limited data on the effect of ALA on glycemia in normoglycemic subjects, which has generally been evaluated on small sample sizes of subjects or in observational studies, the aim of this study was to evaluate the safety and efficacy of the reduction of different forms of pain by ALA treatment, administered orally for two months at two doses (800 and 400 mg/day) as part of a monocentric, randomized, double-blind placebo-controlled clinical trial. As far as the safety assessment of ALA is concerned, its effect on glycemia was evaluated as the primary outcome in the recruited normoglycemic subjects. Moreover, the adverse reactions (ARs) were evaluated using techniques recommended by the Italian National Institute of Health, Ministry of Health (www.vigierbe.it) to collect and report any suspected ARs to food supplements. ALA efficacy was evaluated in different idiopathic pain (arthralgia, neuropathic pain, and myalgia in which pain was not secondary to clinically evident tissue damage) in which subjects needed pain relief but could not or did not want to take pain killing drugs, as pain is associated with significant functional disability to the point of interfering with quality of life and daily activities. In addition, hepatic and renal functions were monitored.

2. Materials and methods

2.1. α-lipoic acid (ALA) and placebo

The α-lipoic acid (ALA) food supplement and placebo were produced by S.I.I.T. (Trezzano sul Naviglio, Italy), with European specifications for contaminants and microbiologic limits. The ALA food supplement consisted of tablets containing 400 mg of α-lipoic acid and excipients (dicalcium phosphate, microcrystalline cellulose, polyvinylpolypyrrolidone, croscarmellose sodium, silicon dioxide, vegetable magnesium stearate, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, acetylated monoglycerides, gum lacquer, hydroxypropyl methyl cellulose) while the placebo only contained the inert excipients (dicalcium phosphate, microcrystalline cellulose, silicon dioxide, magnesium stearate, glyceryl dibehenate, talc, calcium carbonate, cross-linked sodium carboxymethylcellulose, hydroxypropyl methylcellulose, polyvinylpolypyrrolidone, gum lacquer, povidone, acetylated mono- and diglyceride esters, stearic acid, titanium dioxide). Both the ALA food supplement and placebo were packaged in white containers of 60 tablets each, indistinguishable in appearance, color, and flavor. The net weight of ALA food supplement and placebo capsules was managed by means of Metrostat statistical software, in agreement with Italian law (e.g. Legge 25 ottobre 1978 n. 690) and standard UNI ISO 2859.

Upon receipt of the ALA food supplements and placebo at the trial center, the shipment was registered ensuring that the information on the packing slip (inside and outside containers) was an accurate match with what had been sent to the site, including the amount, batch numbers, manufacturing date, expiry date, name of manufacturer, quantity and storage conditions. Both the ALA food supplement and placebo were stored in a locked cabinet in a locked room at environmental temperature, accessible only to essential research personnel. The entry and exit logbook and food supplement accountability logbook were kept and reviewed by the monitor periodically.

2.2. Clinical trial design

A monocentric, randomized double-blind placebo-controlled clinical trial was performed by COMEGEN - Società Cooperativa Sociale (Naples, Italy) to evaluate the safety and efficacy of ALA food supplementation on an adult population suffering from idiopathic pain (arthralgia, neuropathic pain, and myalgia with unknown etiology) diagnosed through a check-up by physicians, recruiting those patients which turned to their general practitioner for an alternative pain relief prescription, as they could not or did not want to take analgesic drugs for the pain relief necessary to increase their quality of life.

The study was double-blind, both for the investigating physician and for the enrolled subjects. The participants received oral and written information concerning the study before they gave their written consent. Protocol, letter of intent of volunteers, and synoptic documents regarding the study were submitted to the Ethics Committee of A.S.L. Napoli 1 Centro. The study was approved by the Ethics Committee (protocol number 532, 19 November 2020) and carried out in accordance with the Helsinki declaration of 1964 (as revised in 2000). This study is listed on the ISRCTN registry (https://www.isrctn.com/ISRCTN89876422).

The clinical trial duration was 6 months. Participants underwent two visits (baseline = t0 and after 2 months = t1) in an outpatient setting. At the baseline visit (t0) information on the sociodemographic and clinical characteristics of the subjects was collected and reported in the case report form (CRF). Numerical rating scale (NRS) and visual analogue scale (VAS) results were reported in the CRF at t0 and after 2 months (t1) for each subject, along with fasting blood glucose assessment, renal and hepatic toxicity assessment by blood test for the evaluation of creatinine (CRE) level, serum glutamic pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT).

Moreover, at the time of enrollment (t0), each subject was given a form to complete based on that used by Italian Phytovigilance System (IPS), to report the possible ARs after the ingestion of food supplements. The forms were collected at the end of the clinical study (t1).

In the clinical study, the 210 subjects enrolled were divided into three groups (70 subjects for each group). In specific, these consisted of subjects assuming the daily dose of 800 mg/day of ALA (two tablets of 400 mg, group 1); subjects assuming 400 mg/day of ALA (one tablet of ALA and one tablet of placebo, group 2); and subjects assuming placebo (two tablets of placebo, group 3).

At the end of the baseline visits, a randomization sequence was generated by a statistician using STATA 16 software (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) and the randomization list was kept hidden. The subjects were assigned to each of the three treatment groups (ALA 800 mg/day, ALA 400 mg/day, and placebo) casually and by simple randomization (1:1:1 allocation ratio). This procedure minimizes any systematic differences between the characteristics of the studied groups (selection bias). It was not used for stratification or blocking. The concealment of the randomization list protected the allocation sequence until the assignment, and was stored at a secured location in the Department of Pharmacy, University of Naples Federico II. The allocation sequence was kept hidden from the recruiting physician and evaluated participants using progressively numbered, opaque, sealed, and stapled envelopes prepared by an investigator with no clinical involvement in the trial. The corresponding envelopes were opened only after the enlisted participants completed all baseline assessments and signed informed consent. ALA food supplement and placebo were prepacked in white containers of 60 tablets. Each container was consecutively numbered for each participant according to the randomization list. Each subject was assigned an order number and received the tablets in the corresponding prepacked containers.

2.3. Outcomes of the study

The primary outcomes of the study were the safety and efficacy of ALA oral administration to normoglycemic subjects with primary neuropathic pain, idiopathic myalgia or arthralgia, who needed an alternative treatment to traditional analgesics as they could not or did not want to take pain medications. Two dosages of ALA (400 mg/day and 800 mg/day) were used in the study in order to demonstrate the efficacy of the lowest dose (400 mg/day), and to confirm the efficacy and safety of the maximum dose (800 mg/day). In particular, as far as ALA safety is concerned, the effect of ALA supplementation on fasting blood glucose was determined in the recruited normoglycemic or mild dysglycemic subjects. The other primary outcome, regarding the evaluation of the efficacy of pain reduction from ALA oral supplementation after two months of treatment, was evaluated using validated questionnaires, such as the Numerical Rating Scale (NRS) and the Visual Analogue Scale (VAS). The NRS is an unidimensional measure of pain intensity in which the subject indicates the intensity of the pain by drawing a circle on the number that best describes it. The instrument is represented by a horizontal line on which a scale of values between 0 and 10 are indicated, corresponding to "no pain" and "worst pain imaginable," respectively [30]. Higher scores indicate greater pain intensity. The minimal perceptible clinical improvement (MPCI) is a 2 point or a 30% reduction on the pain NRS scores [31,32].

The VAS is another pain assessment tool, used for a variety of purposes and in the assessment of general pain. It consists of a 100 cm paper strip, with the two end points of "no pain" and "worst pain I can imagine" at either end. The subject must mark the level of perceived pain on the strip. The following cut-off points are recommended for the pain VAS: no pain (0–4 cm), mild pain (5–44 cm), moderate pain (45–74 cm), and severe pain (75–100 cm) [33].

The secondary outcome was the evaluation of possible ARs registered by filling in a form, specifically prepared according to IPS standards, for the reporting of suspected ARs that may occur after the intake of food supplements. This serves to assess the severity of the ARs, and the causal relationship between the oral administration of ALA and/or any concomitant therapy, and the ARs.

In addition, renal and hepatic functions were monitored for two months following the oral administration of ALA, through the determination of blood tests to evaluate CRE, SGPT, and SGOT, performed at t0 and t1.

2.4. Study population

210 Subjects aged 18–75 and of either sex, with a fasting glycemia below 105 mg/dl at recruitment and with signed informed consent, were enrolled by the general practitioners of Comegen in June 2021 and subdivided into three groups as reported above. Subjects with the need for pain relief, but who were unable or unwilling to take analgesic drugs, were considered eligible for the enrollment if they suffered from a mild to moderate primitive pain with no detectable inflammation, no tissue damage or damage to the nervous system, and no identifiable noxious stimulus (i.e. primitive neuropathic pain, arthralgia with unknown etiology, and idiopathic myalgia). As far as arthralgia and myalgia are concerned, the medical classification list ICD (International Statistical Classification of Diseases and Related Health problems), generated by the World Health Organisation (WHO), was used by the physicians to identify and code the type of pain in the enrolled subjects. ICD-9-CM diagnosis code 719.4 defining “pain in joint” was applied to arthralgia and ICD-9-CM diagnosis code 729.1 was applied to myalgia [34,35].

Pregnant women, women suspected of being pregnant, women who hoped to become pregnant, breastfeeding women, patients with allergies, congenital or acquired immunodeficiency syndrome, fasting glycemia above 105 mg/dl, obesity (BMI > 30 kg/m^2), undergoing pharmacology therapy for diabetes, cardiovascular diseases, systemic chronic disease, analgesic therapy, anti-inflammatory or food supplements for pain, and those considered unsuitable for participation by the physician were excluded from the study.

2.5. Statistical analysis

Sample size calculation was conducted using three 1-β power values (0.80, 0.95 and 0.99), a significance threshold value of α equal to 0.05, and three effect size values (Cohen's f = 0.10, 0.14 and 0.25, respectively). Sample size was determined to be 210 participants (70 each group).

The effect of the treatments on the response variables (NRS, VAS, glycemia, SGOT, SGPT and creatinine), was assessed through a Random Intercept Linear Mixed Model (LMM), where the treatment groups (G1, G2 and G3), the measurement times (t0 and t1), and the age and sex of subjects entered the model as fixed effects. The interaction group × treatment was also added to the fixed effects in order to account for differential patterns of responses of groups to measurements. Finally, subject identity was entered into the model as a random effect, to account for repeated measures within subjects.

In a second analysis, we searched for possible differences in NRS and VAS scores among treatment groups due to pain source (arthralgia or neuropathic pain). To do so, we were able to collect data for a subsample of 198 out of 210 subjects enrolled in the study (G1: 66, G2: 67, G3: 64). On this subsample we ran the same LMM we used for the previous analysis, but updated to evaluate the three-way interaction group × treatment × pain, accounting for differential responses between treatment groups due to the combination of measurement time (t0 and t1) and nature of pain (arthralgia or neuropathic pain).

Analyses were performed using the lme4 (D. Bates, M. Maechler, B. Bolker, S. Walker, Fitting Linear Mixed-Effects Models Using lme4, J. Stat. Soft. 67 (2015) 1–48) and MuMIn (Barton, K. 2020. 'MuMIn': Multi-Model Inference. R Package Version 1.43.17. Available online: https://CRAN.R-project.org (accessed on 2 August 2021) packages in R ver. 4.0.1 (R core Team 2021), and unless otherwise stated, data are reported as means ± standard errors.

3. Results

3.1. Clinical trial

The study flow chart is reported in Fig. 1 according to the CONSORT PRO reporting guideline [36]. The two ALA treated groups consisted of 140 subjects: 26 male (corresponding to 37%) and 44 female (63%) treated with the ALA dose of 800 mg/day (two tablets of 400 mg of ALA), and 29 (41%) male and 41 female (59%) treated with the ALA dose of 400 mg/day (one tablet of 400 mg of ALA and one tablet of placebo). The untreated group consisted of 70 subjects, 25 male (36%) and 45 female (64%), treated with two tablets of placebo. The participants in the three groups had similar sociodemographic characteristics and clinical data with no significant differences. The baseline characteristics of the subjects for each group are summarized in Table 1.

In Table 2 the data regarding the primary and secondary outcomes at baseline and t1 are reported. The study revealed that the two response variables (NRS and VAS) changed among the ALA food supplement groups and the placebo group between the beginning (t0) and the end (t1) of the clinical trial.

Indeed, the results from the LMM applied to the NRS and VAS scale (Table 3) highlighted significant effects over time for the group, time of measurement and group-measurement time interaction, but not for the age and sex of subjects, suggesting that age and gender do not influence these variables.

There was a significant difference in NRS pain scale values between t0 and t1 in each experimental group. In particular, the NRS values in the G1 group significantly decreased from t0 to t1 (-4.55 ± 0.24, $t_{207} = 19.34$, $P < 0.001$, Fig. 2) and the same occurred in the G2 group (-4.25 ± 0.24, $t_{207} = 18.03$, $P < 0.001$, Fig. 2). On the contrary, in the G3 group there were no significant differences in the NRS values between t0 and t1 (-0.04 ± 0.24, $t_{207} = 0.18$, $P = 0.86$, Fig. 2). The random effect between subjects was highly significant in both models ($LR\chi^2 = 45.27$, df=1, $P < 0.001$).

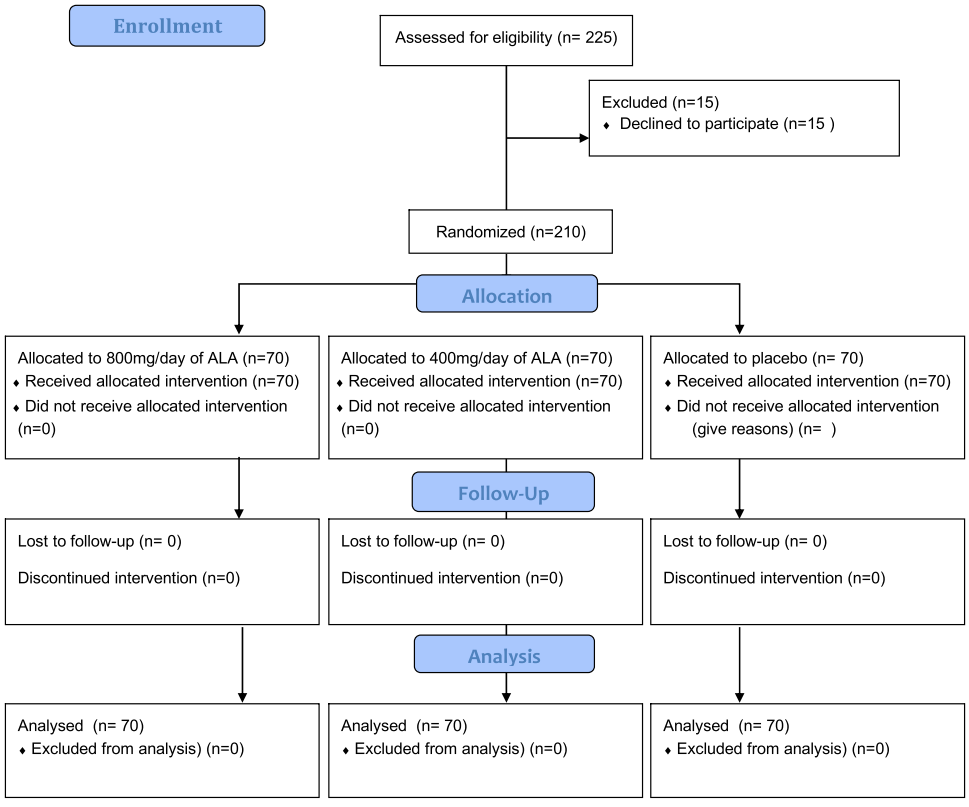

Fig. 1. CONSORT Flow diagram.

Table 1
Characteristics of the study population: demographic and clinical data at baseline.

Characteristic/ Treated Untreated Clinical data	Group 1 (n = 70) Treated with ALA (dose 800 mg/ day)	Group 2 (n = 70) Treated with ALA (dose 400 mg/ day)	Group 3 (n = 70) Untreated (placebo)
Age	Male = 53.5 ± 7.98 Female = 54.2 ± 7.25	Male = 54.6 ± 7.47 Female = 52.7 ± 7.85	Male = 55.7 ± 5.17 Female = 5.8 ± 6.58
Gender	Male = 26 Female = 44	Male = 29 Female = 41	Male = 25 Female = 45
Type of pain (n° subjects):			
arthralgia	50	45	46
neuropathic pain	16	22	19
idiopathic myalgia	4	3	5
NRS	6.2 ± 2.2 (3–10)	6.2 ± 2.4 (3–10)	6.0 ± 2.1 (3–10)
VAS	57.7 ± 24.7 (1–100)	59.9 ± 23.7 (1–100)	62.4 ± 26.2 (1–100)
Glycemia	82.3 ± 11.5 (70–104)	86 ± 11.1 (70–105)	87.5 ± 10.9 (70–104)
SGOT	37 ± 8 (24–50)	37 ± 8 (24–50)	37 ± 8 (24–50)
SGPT	37 ± 8 (24–50)	37 ± 6 (24–49)	37 ± 6 (24–49)
Creatinine	0.95 ± 0.10 (0.80–1.10)	0.93 ± 0.08 (0.80–1.09)	0.96 ± 0.09 (0.81–1.10)

For the VAS pain scale, the results were similar to the NRS scale. Indeed, the model showed significant effects between the groups, times of measurement and their interaction, but not for age and sex of subjects (Table 2). In particular, the values on the VAS scale in G1 significantly decreased from t0 to t1 (-51.07 ± 2.15, $t_{207} = 23.80$, $P < 0.001$, Fig. 2) passing from moderate to mild pain (Table 1). The same thing occurred in group G2 (-35.37 ± 2.15, $t_{207} = 16.49$, $P < 0.001$, Fig. 2), passing through moderate to mild (Table 1). As in the previous analysis, for G3 there was no significant difference in the intensity of pain VAS values from t0 to t1 ($+1.00 \pm 0.24$, $t_{207} = 0.47$, $P = 0.64$, Fig. 2) which remained moderate until the end of trial. The random effect between subjects was still highly significant ($LR\chi^2 = 118.43$, $df = 1$, $P < 0.001$).

As reported before, one of the mechanisms of action of ALA is the decreasing of glycemia through insulin metabolic pathways, glucose uptake and glycogen synthesis. As far as fasting blood glucose levels are concerned, a significant effect was detected only for the interaction group × measurement, while no significant effect was found for the measurements or age and sex of subjects (Table 3). However, the variations in glycemia identified by the LMM between t0 and t1 were only in the order of one or two points (Fig. 2): variations were $+1.13 \pm 0.29$ ($t_{207} = 3.83$, $P < 0.001$) in G1 and -0.80 ± 0.29 ($t_{207} = 2.72$, $P = 0.0072$) in G3, while in G2 the variation was not significant (-0.26 ± 0.29, $t_{207} = 0.87$, $P = 0.40$). The random effect was found to be highly significant ($LR\chi^2 = 615.18$, $df = 1$, $P < 0.001$).

The LMMs did not identify any significant effect on hepatic and renal functions (Table 4, Fig. 2). However, the random effect between subjects was highly significant in all cases ($LR\chi^2 > 363.97$, $df = 1$, $P < 0.001$).

During the two months of treatment, no subjects reported ARs related to administration of ALA in either dose, including the absence of allergies, and the principal investigator judged that the application of ALA tablets can be considered to be well tolerated.

Finally, the LMMs aimed at detecting possible differences in NRS and VAS scores among treatment groups based on the source of pain (i.e., arthralgia or neuropathic pain), did not reveal any significant effect, as the three-way interaction group × measurement × pain was not significant for both models (NRS: $F2192 = 0.217$, $P = 0.81$; VAS: $F2192 = 1.109$, $P = 0.33$). The two-way interaction group × pain was

Table 2
Primary and secondary outcomes at baseline (t0) and t1.

Variable	t0	t1
NRS		
G1	6.2 ± 2.2 (3–10)	1.7 ± 0.8 (0–4)
G2	6.2 ± 2.4 (3–10)	1.9 ± 1.0 (0–5)
G3	6.0 ± 2.1 (3–10)	6.0 ± 2.1 (1–10)
VAS		
G1	57.7 ± 24.7 (10–100)	6.6 ± 6.8 (0–30)
G2	59.9 ± 23.7 (10–100)	24.5 ± 15.2 (0–80)
G3	62.4 ± 26.2 (10–100)	63.4 ± 26.9 (10–100)
Glycemia		
G1	82.3 ± 11.5 (70–104)	83.4 ± 10.8 (70–105)
G2	86 ± 11.1 (70–105)	85.7 ± 10.4 (70–108)
G3	87.5 ± 10.9 (70–104)	86.7 ± 10.2 (70–105)
SGOT		
G1	37 ± 8 (24–50)	37 ± 8 (24–50)
G2	37 ± 8 (25–50)	37 ± 8 (24–50)
G3	37 ± 8 (25–50)	36 ± 8 (25–50)
SGPT		
G1	36 ± 8 (25–50)	36 ± 8 (25–50)
G2	38 ± 8 (25–50)	38 ± 7 (25–50)
G3	37 ± 6 (25–49)	37 ± 6 (25–50)
Creatinine		
G1	0.95 ± 0.10 (0.80–1.10)	0.94 ± 0.09 (0.78–1.10)
G2	0.93 ± 0.08 (0.80–1.09)	0.92 ± 0.080 (0.80–1.10)
G3	0.96 ± 0.09 (0.81–1.10)	0.96 ± 0.09 (0.81–1.10)

Table 3
Results for the LMM models for the analysis related to the primary outcome of the study.

Model	F	df	P
NRS			
Measurement	499.22	1207	**< 0.001**
Group	35.03	2205	**< 0.001**
Gender	1.96	1205	0.16
Age	1.09	1205	0.30
Measurement × Group	114.33	2207	**< 0.001**
VAS			
Measurement	528.80	1207	**< 0.001**
Group	41.77	2205	**< 0.001**
Gender	1.01	1205	0.31
Age	1.98	1205	0.16
Measurement × Group	155.01	2207	**< 0.001**
Glycemia			
Measurement	0.02	1207	0.89
Group	2.87	2205	0.06
Gender	1.04	1205	0.31
Age	0.03	1205	0.87
Measurement × Group	11.39	2207	**< 0.001**

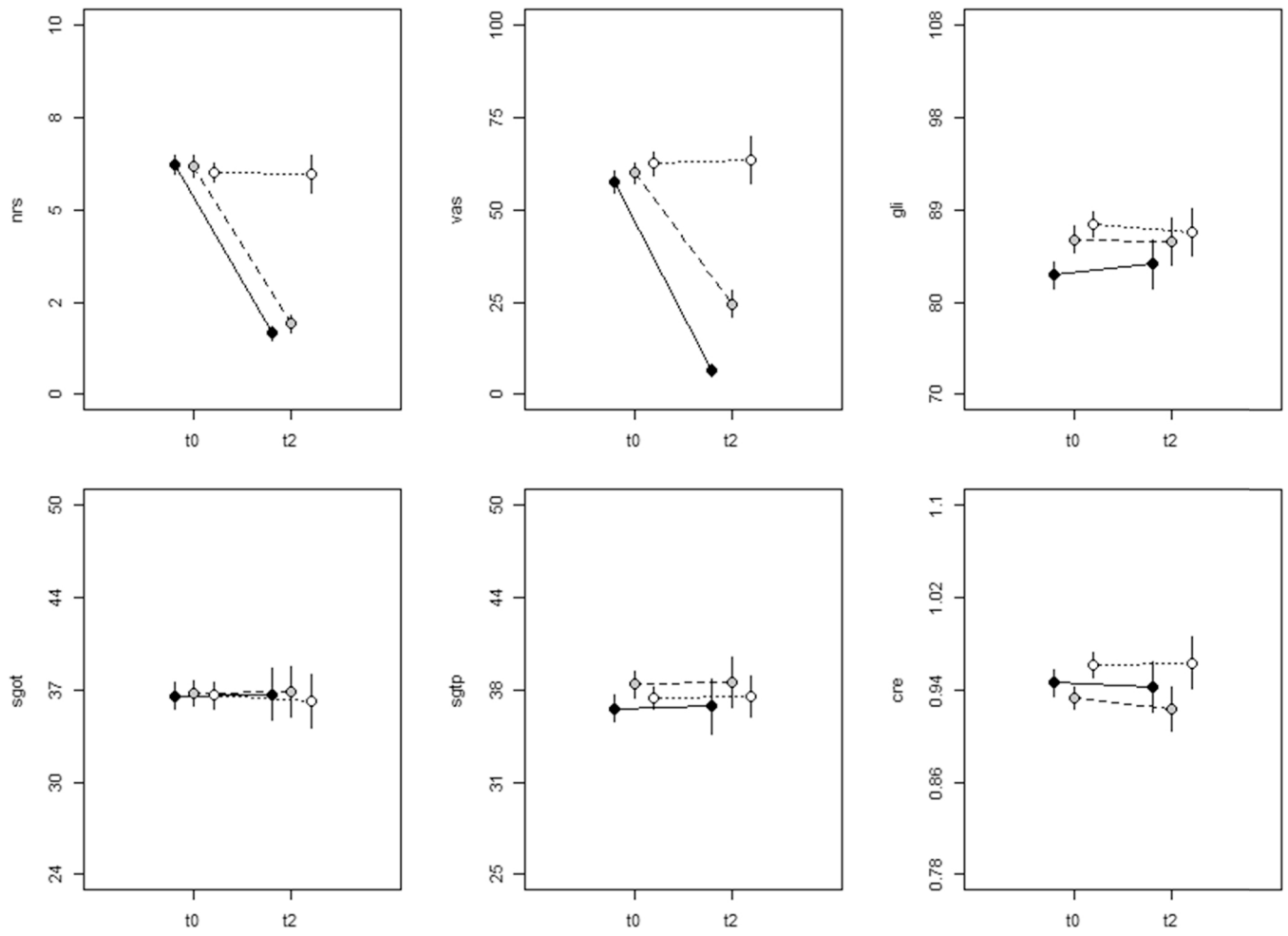

Fig. 2. Variations of the six response variables evaluated at t0 and t1 in the three experimental groups (black and continuous line: G1; gray and dashed line: G2; blank and speckled line: G3). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Results of the LMM models for the hepatic and renal toxicity analysis.

Model	F	df	P
SGOT			
Measurement	0.19	1207	0.66
Group	0.07	2205	0.93
Gender	< 0.01	1205	0.99
Age	0.11	1205	0.74
Measurement × Group	1.12	2207	0.33
SGPT			
Measurement	0.61	1207	0.44
Group	0.93	2205	0.39
Gender	0.44	1205	0.51
Age	0.76	1205	0.38
Measurement × Group	< 0.01	2207	0.99
Creatinine			
Measurement	1.74	1207	0.19
Group	2.73	2205	0.07
Gender	0.33	1205	0.57
Age	< 0.01	1205	0.92
Measurement × Group	1.30	2207	0.27

also not significant in both models (NRS: F2190 = 1.861, P = 0.16; VAS: F2190 = 0.133, P = 0.86).

4. Discussion

In this monocentric, randomized, double-blind, placebo-controlled clinical trial, the safety and the efficacy in the reduction of mild or moderate pain (arthralgia, neuropathic pain, and fibromyalgia, with unknown etiology) of an ALA food supplement, administered orally for two months at doses of 400 mg/day or 800 mg/day, were studied in 210 normoglycemic subjects, which turned to their general practitioner for the prescription of pain relievers alternative to analgesic drugs commonly used to treat pain, as reported in the first (i.e. aspirin, paracetamol and the non-steroidal anti-inflammatory drugs) and the second (weak opioids such as codeine) analgesic step of the WHO analgesic ladder [37].

ALA treatment was found to be able to significantly reduce pain intensity as measured by the two most commonly used unidimensional pain intensity scales, NRS and VAS, at both doses, with the higher dose being more effective than the lower one. Although VAS highlighted a greater difference in pain relief between the two ALA doses, these scales showed good correlation in agreement with the conclusions reported by systematic reviews on comparison of pain scales [38,39]. The results of this investigation are all the more significant considering the need for novel pain treatments alternative to commonly used drugs, which often fail in the achievement of an adequate pain management. Breivic et al. studied current treatment practices and levels of satisfaction with treatment in a large-scale computer-assisted telephone survey including 4839 subjects suffering from chronic pain in 15 European Countries and Israel. The results showed that 64% of those taking prescription drugs found that their pain medication was inadequate and, of the 48% of chronic pain suffering subjects not taking pain medication, 14% had stopped due to side effects [40].

The ALA food supplement was found to be effective independently from the type of pain (arthralgia, neuropathic pain, and myalgia with unknown etiology). In this clinical trial 57 subjects were affected by neuropathic pain, 141 subjects by arthralgia, and only 12 subjects by myalgia. As far as neuropathic pain is concerned, the obtained results are in line with the literature data on the efficacy and safety of ALA in the treatment of neuropathy caused by diabetes, and extend the use of ALA to idiopathic neuropathy. Neuropathic pain, defined by the International Association for the Study of Pain (IASP) as: "*pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory nervous system*" [41], affects about 7–10% of the general population, being more frequent in subjects with age > 50 years. Neuropathic pain has a complex etiopathogenesis, with diabetes being known as the most common cause of neuropathic pain, which affects about one third of diabetic patients. Although many causes are considered responsible for neuropathic pain (i.e. mechanical-compressive, traumatic, viral and inflammatory causes), in many cases (about 20–30%) the etiology of neuropathy remains idiopathic [42]. Especially in its idiopathic forms, the management of neuropathic pain is a real challenge for physicians as they cannot treat the causes underlying this symptom, and can only relieve the pain with symptomatic drugs. In fact, the most common interventions used to treat diabetic neuropathy (lifestyle improvement, intervention on glycemic control, and pathogenesis-oriented pharmacotherapy, which exert effects on the processes by which hyperglycemia leads to cell damage) cannot be used, and only symptomatic pain relief can be prescribed [43]. The drugs used to relieve neuropathic pain include tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs) and calcium-channel anticonvulsants and opioids, which are limited in their effectiveness and have considerable side effects [44]. A quite recent meta-analysis [45] on the adverse effects of antidepressant drugs used in pain relief in randomized controlled trials showed that amitryptiline, a tryciclic antidepressant, induces adverse effects in a percentage ranging from 52% to 100% of treated patients. Its adverse effects include dry mouth, drowsiness, urinary difficulty, constipation, sweating, headache, irritability, palpitations, diarrhea, blurred vision, dizziness, edema, gastritis, thirst, tachycardia, weight gain, and nausea. In the same systematic review, the adverse effects (i.e. nausea, vomiting, dizziness, and somnolence) of venlafaxine (SNRI) were evaluated, showing that the percentage of subjects suffering from adverse effects ranges from 14% to 100% of the treated patients. As far as calcium-channel anticonvulsants are concerned, the most common adverse effects of anticonvulsants are sedation and cerebellar symptoms (nystagmus, tremor and incoordination), occurring quite frequently [46].

In this study, 141 subjects suffering from arthralgia with unknown etiology were recruited. Arthralgia, the pain in one or multiple joints (i.e. hands, knees, hips and spine), is estimated to be the second of the ten most common reasons for a visit to a physician. It can be due to either inflammatory or non-inflammatory forms of arthritis. About 50% of subjects with arthralgia or poly-arthralgia have an unclassifiable condition, not accompanied by typical signs of inflammation and extra-articular symptoms. At the end of this study, subjects with arthralgia treated with an ALA food supplement had an improvement in pain respect to the placebo group, without any clinically significant changes in glycemia and without any indication of adverse effects. To our knowledge, this clinical trial is the first that demonstrates an effect of ALA food supplements in non-inflammatory forms of arthralgia. The unclassifiable forms of arthralgia are generally transient, of little clinical significance and may not require a pharmacologic treatment, going into remission within a year. Nevertheless, when the treatment of the joint pain is required, as pain induces significant emotional distress and interferes with activities of daily life and participation in social roles, the most common drug used to relieve pain is acetaminophen (N-acetyl para-aminophenol or paracetamol), which is the most widely used as an over-the-counter non-opioid analgesic agent used to treat mild to moderate pain. Although the common perception is that acetaminophen is an extremely safe drug, it can however cause serious adverse effects (i.e.) and is responsible for 56,000 emergency department visits, 2600 hospitalizations, and 500 deaths per year in the United States (with fifty percent of these being due to unintentional overdoses) and is the second most common cause of liver transplantation worldwide [47]. The most common adverse effects are skin rash, hypersensitivity reactions, nephrotoxicity, hepatotoxicity (increased aminotransferase activity at therapeutic doses, hepatic failure in the case of overuse, enhanced previous liver damage caused by alcohol consumption), hematological (i.e. anemia, leukopenia, neutropenia, pancytopenia), metabolic (hyperglycemia, increased bilirubin and alkaline phosphatase) and electrolyte (i.e. decreased serum bicarbonate, decreased concentrations of sodium and calcium, hyperammonemia, and hyperchloremia) disorders [48], and liver injury. When acetaminophen fails to relieve pain, non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs, although these exert many adverse effects (i.e. gastrointestinal bleeding, renal toxicity, and hypertension), being responsible for about 30% of hospitalizations due to adverse drug reactions. It is estimated that 5000–16,500 annual deaths in the United States and 400–1000 deaths in the United Kingdom are directly related to upper gastrointestinal ulceration and bleeding caused by NSAIDs [49].

Finally, 12 subjects with a further type of pain lacking an organic basis, such as fibromyalgia, were recruited. Fibromyalgia, which affects between 2% and 4% of the general population, mainly consisting of women, is characterized by generalized chronic pain in the absence of clinically evident structural abnormalities explaining said pain. The low number of recruited subjects suffering from idiopathic fibromyalgia made it impossible to perform an appropriate statistical analysis, although pain improvement in ALA treated subjects was registered. Contradicting results were achieved by a recent randomized, placebo-controlled, crossover trial, which evaluated the effect of ALA on pain intensity, measured with NRS, in 27 subjects (5 males and 22 females; age range: 25–74 yrs) suffering from fibromyalgia, treated for 4 weeks with ALA at increasing doses ranging from 300 mg/day in the first week to 1800 mg/day in the fourth week. Across all these subjects, no statistically significant differences were found between placebo and ALA groups, nevertheless, the post hoc exploratory subgroup analysis showed a significant difference between placebo male subjects and ALA treated male subjects, probably due to gendered differences in the pharmacokinetics of ALA. Considering the limited efficacy, and above all the serious adverse effects, of the four drug classes (i.e anti-epileptic drugs, tricyclic anti-depressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors) used to treat fibromyalgia, it is necessary to carry out large-scale population clinical trials to define the actual effects of ALA in the reduction of pain due to fibromyalgia.

In terms of side and adverse effects of ALA, the ALA food supplement treated subjects did not show any clinically significant changes in glycemia or any indication of adverse effects. Our results are in agreement with those obtained by Gosselin et al. who studied the effect of ALA oral supplementation (600 mg/mL for 30 days) on plasmatic glucose levels in 12 pre-diabetic subjects showing a glucose level of 102.1 ± 5 mg/dL at baseline, in a randomized, double-blinded, placebo controlled crossover clinical trial. Compared to the placebo groups, the ALA treated subjects showed a statistically insignificant decrease in serum glucose, and a statistically significant decrease in insulin and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index, suggesting that ALA also exerts its properties in healthy subjects with mild dysglycemia [50]. Moreover, in a clinical trial on the improvement of migraine in patients with insulin resistance, Cavestro et al. studied the effects of ALA oral supplementation (400 mg/day for 6 months) on serum glucose, used as secondary outcome, at baseline and after 6 months in 32 normo-glycemic subjects, with the results showing no variation in this parameter [13]. In 2020, Derosa et al., in a retrospective, observational study enrolling 322 patients treated with different dosages of ALA (i.e. 400, 600, 800 and 1200 mg/day), concluded that the chronic use (4

years) of ALA is well tolerated at all dosages, with an improvement in glycemic status only at high dosages in disglycemic subjects [51]. Recently, in 2021, Gatti et al. [52] conducted the first real world assessment of the safety profile of ALA-containing products by analyzing spontaneous reports of suspected adverse reactions (ARs) collected from March 2002 to February 2020 by the IPS, coordinated by the Italian Institute of Health. Of the 2147 total reports found, 116 reports (about 5.4% of the total number of collected reports) regarded the ARs to ALA-containing products, and of these 15 reports (about 0.7% of the total number of collected reports) showed a definite causality assessment. In accordance with WHO-VigiBase data, this study showed that the ARs consist of cutaneous, gastrointestinal, nervous and immune disorders with varying degrees of seriousness. Skin (44.9%) and gastrointestinal disorders (10.8%) were the most frequently represented ARs. Skin and subcutaneous tissue disorders were found to be significantly predominant in non-serious events (52.5% vs. 30.9%; $p = 0.004$). Overall, 45 (38.8%) cases were classified as serious, but no fatal cases were reported by the IPS. In particular, ten cases of IAS, mostly represented as serious cases, were registered (about 0.5% of the total number of collected reports), among which only one case was considered confirmed (about 0.05% of the total number of collected reports) according to the WHO system for standardized case causality assessment. In the letter to the Editor of the Clinical Nutrition Journal published in 2020 [53] some concerns about the interpretation of these data were reported, concluding that warning for ALA should be cautious as the high ALA safety profile is reported in large meta-analyses [6,54]. In particular, the meta-analysis published by Fogacci et al. showed that ALA was not associated with an increased risk of any treatment-emergent adverse event ($p > 0.05$), being ALA supplementation safe in different populations groups such as smokers, pregnant women, children/adolescents, diabetics, heart patients [54].

Regarding the link between IAS and ALA treatment, in 2021 the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked by the European Commission to deliver an opinion on the relationship between the intake of ALA and the risk of IAS. In the opinion, EFSA reported data published by Yamada et al. [55] in 2020, indicating that the incidence of IAS in the general Japanese population was 0.017 cases per 100.000 inhabitants in the years 2017–2018, while the incidence in the Caucasian population was lower than that found in the Japanese population, likely due to the lower presence of the Human Leukocyte Antigen HLA-DR4, and in particular the alleles DRB1 * 04:03 (responsible for most Caucasian cases) ranging from 0.4% to 3.9% in European Countries and from 1.6 to 12.3 in Japan and South Korea. The results from the comprehensive literature search performed by EFSA on the published case reports in the English language yielded 49 cases of IAS linked to ALA intake worldwide. Of these 49 cases, 20 were observed in Europe. 22 cases out of the 49 did not report the symptoms involved, and in 12 cases the symptoms were serious but not lethal. The EFSA NDA panel concluded that "*Based on the limited data available and the low prevalence of IAS in Europe the risk associated with the development of IAS following consumption of ALA cannot be quantified precisely neither for the general population overall nor for sub-groups or individuals with genetic susceptibility*." [56].

Thus, while the pharmacological treatment of pain is considered to be the first and the second analgesic step of the WHO analgesic ladder, the comparison between the extent and incidence of the adverse effects of analgesic drugs and ALA taken orally through food supplements is clearly in favor of the latter.

This work has certain limitations and strengths. First, a follow up was not performed beyond the 2 months of treatment, making it impossible to learn about any longer-term effects of ALA supplementation on pain relief. Moreover, the VAS and NRS methods used to estimate the severity of pain and estimate the extent of pain relief, only evaluate the intensity of pain, which is only one component of the pain experience, and do not consider the complexity of the pain experience. The third limitation regards the low number of subjects suffering from idiopathic myalgia, which made it impossible to assess the therapeutic effect on this type of pain.

On the other hand, the major strength of this clinical trial is the robustness of the experimental design in the assessment of safety of ALA supplementation, as the effect of ALA on glycemia for a statistically significant number of normoglycemic subjects was assessed as the primary outcome of this interventional study, and is not a retrospective assessment.

5. Conclusion

In conclusion, the management of idiopathic pain is a real challenge for physicians, as they cannot treat the causes underlying this symptom but can only relieve the pain with the use of symptomatic drugs which generally have a good and rapid efficacy, although in some cases possess limited efficacy and considerable side effects. Thus, in the absence of a diagnosis of pain-causing disease, the use of an ALA food supplement, which according to current legislation is not intended to treat or prevent diseases in humans and is addressed towards the general population, could be considered as a feasible option both in the context of general practice and in specialist settings where appropriate, bearing in mind the safety of ALA supplementation in comparison with that of commonly-used analgesic drugs and its efficacy in pain treatment. In the future, further larger-scale studies will be necessary to consolidate the promising findings of the present study, in addition to offering proper information for practicing physicians about the appropriate uses of this treatment approach.

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Author contributions

MDA, GP, CE, and RP designed the clinical study, analyzed and interpreted the data; MDA, CE and EUG drafted the manuscript; GP conducted the clinical study; CE, EUG, CS, MD and ADM wrote the documents for the Ethics Committee, monitored the clinical study, and collected and analyzed the data; RS performed the statistical analysis;. All authors revised and gave their final approval for publication.

Conflict of interest statement

All authors declare no conflict of interest.

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