

Safety and efficacy of an add-on therapy with curcumin phytosome and piperine and/or lipoic acid in subjects with a diagnosis of peripheral neuropathy treated with dexibuprofen

Francesco Di Pierro¹
Roberto Settembre²

¹Scientific Department, Velleja Research, Milan, Italy; ²Neurosurgery Department, Di Venere Hospital, Bari, Italy

Abstract: We conducted an 8-week, open, randomized controlled clinical trial on 141 subjects affected by neuropathic pain to investigate the role of an adjunctive therapy added to the administration of dexibuprofen (400 mg twice a day) and based on a multi-ingredient formula (Lipicur), consisting of lipoic acid plus curcumin phytosome and piperine, in patients with a diagnosis of lumbar sciatica, lumbar disk herniation, and/or lumbar canal stenosis (96 subjects), or with carpal tunnel syndrome (45 subjects). A total of 135 participants completed the study. Treatment with the multi-ingredient formula (Lipicur) reduced neuropathic pain by more than 66% in both conditions (subjects with lumbar sciatica and with carpal tunnel syndrome), and these reductions were statistically significant. Moreover, the treatment reduced dexibuprofen use by about 40%. An add-on therapy with only lipoic acid has not shown any significant results. On the basis of its safety and efficacy, Lipicur could be considered an effective complementary therapy to be added to conventional treatments to achieve better efficacy in reducing neuropathic pain.

Keywords: curcumin, phytosome, piperine, dexibuprofen, neuropathic pain

Introduction

Peripheral neuropathy is a particularly widespread clinical condition, whose overall prevalence, approximately 4%, reaches 8% in individuals over 55 years of age.¹ Peripheral neuropathy affects nerve fibers in varying ways, but because in general it first attacks sensory fibers, in the initial stages of the disease the most common symptoms are paresthesias and pain.² Neuropathic pain is caused by such events as compression, infiltration, ischemia, or metabolic damage to neurons.³ The mechanical compression of the nerve triggers inflammatory, immunological, and ischemic processes that are responsible for the damage to nervous fibers and, clinically, for neuropathic pain.⁴ Oxidative stress seems to play an important role in the pathogenesis of neuropathic pain. In fact, it is both the result of an altered mechanism of oxygen reduction, with consequent excessive production of free radicals, and a consequence of ischemia, which in turn can reduce the supply of nutrients to nerve cells with necrosis of Schwann cells.^{5,6} These etiopathogenic processes are found in both lumbar sciatica and carpal tunnel syndrome. Lumbar sciatica is a form of peripheral neuropathy characterized by lumbar or lumbosacral spine pain that radiates to the buttocks, and in the lower limbs to the thigh (involving femoral nerve roots L2/L3) or beyond the knee and foot (L4/L5/S1).^{7,8} Lumbar pain is quite frequent; it

Correspondence: Francesco Di Pierro
Scientific Department, Velleja Research,
23 Viale Lunigiana, Milan 20125, Italy
Tel +39 349 552 7663
Fax + 39 0523 511 894
Email f.dipierro@vellingaresearch.com

has been estimated that 70%–85% of individuals have suffered from it during their lives. In 97% of cases, it is of a mechanical nature, while a different (neoplastic, infective, visceral) etiopathogenesis is very rare (3% approximately).⁹ Chronic lumbar sciatica, persisting for over 3 months, is most frequently caused by chronic degenerative problems, and results in a reduced quality of life, heavily affected by pain and disability.^{10–15} Carpal tunnel syndrome is the most common of the canalicular syndromes (entrapment of a peripheral nerve). In this case, it involves the median nerve, which is compressed, inside the carpal tunnel, between the transverse ligament and carpal bones. Pain increases in intensity with the progress of the disease. Consequently, optimal handling of symptoms is essential to prevent a lower quality of life and the loss of hand function.^{16–22} The guidelines for treatment of neuropathic pain consider the use of different classes of drugs, like analgesics, antidepressants, and anticonvulsants.^{23–27} A complete therapeutic approach should consider both a support to nerve efficiency and the control of symptoms.²⁸ The former can be attained by counteracting the etiopathogenic effects derived from the nerve compression and consequent ischemia through pharmacological aids. To this end, several authors have proposed the use of lipoic acid, an endogenous antioxidant that is supposed to provide neuroprotection.^{29–32} Another potential candidate seems to be curcumin, a polyphenol extracted from *Curcuma longa* roots and endowed with anti-inflammatory properties; the latter is due to modulation of different transcription factors, which in turn are responsible for the decreased synthesis of proinflammatory cytokines (interleukin [IL]-1, IL-2, IL-6, and tumor necrosis factor- α) and play a role in anticyclooxygenase 2 and anti-NO synthase.^{33–35} Unfortunately, curcumin exhibits poor oral bioavailability, caused by limited intestinal absorption and massive liver metabolism through phase 2 enzymes.³⁶ Its conjugation with a lipid vector^{37–40} and association with piperine⁴¹ reduce the kinetic limitations of curcumin and make its oral use more effective. We thus decided to investigate the role of an adjunctive therapy, based on lipoic acid and curcumin, in patients with a diagnosis of lumbar sciatica, lumbar disc herniation and/or lumbar canal stenosis, or with carpal tunnel syndrome.

Materials and methods

Study design

This 8-week, open, randomized, controlled clinical trial was conducted in the field of routine clinical practice, following the relevant international guidelines and in line

with the principles outlined in the Declaration of Helsinki. It was carried out in a single center in Italy (Department of Neurosurgery, Di Venere Hospital, Bari) between October 2011 and July 2012. A total of 141 patients diagnosed with lumbar disc herniation and/or lumbar canal stenosis (96 subjects) or carpal tunnel syndrome (45 subjects) were enrolled. All patients provided written informed consent to participate in this study after a full explanation of the study had been given. A total of 135 participants completed the study.

Criteria

Inclusion criteria were: (1) informed consent and privacy agreement signed and returned; (2) a diagnosis of chronic peripheral neuropathy and specifically lumbar disc herniation and/or lumbar canal stenosis or carpal tunnel syndrome; and (3) a negative pregnancy test for female patients. Exclusion criteria were: (1) refusal to sign the informed consent or privacy agreement; (2) moderate-to-severe liver disorders, including serum alanine aminotransferase exceeding 120 IU/L, aspartate aminotransferase exceeding 80 IU/L, and/or abnormal renal function (serum creatinine exceeding 115 $\mu\text{mol/L}$); (3) severe heart dysfunction (New York Heart Association class III or higher); (4) a diagnosis of gastroesophageal reflux disease or any other diagnosed gastroduodenal disorder; (5) psychiatric disease or severe infection; (6) pregnancy or planned pregnancy; and (7) recent use (in the past 15 days) of anti-inflammatory and/or analgesic drugs.

Concomitant therapies

The following concomitant therapies were admitted: statins, hypoglycemics, Eutirox, ticlopidine, warfarin, Ca antagonists, beta-blockers, antibiotics, gastroprotectants, and the contraceptive pill.

Study protocol and treatments

All participants were advised to follow their usual diet and encouraged to continue following their usual standardized physical activity (in the case of a diagnosis of carpal tunnel syndrome). All the enrolled subjects were randomized by an independent investigator, using a computer-generated random-number table, to any of three groups: one receiving two tablets/day (8 am and 8 pm) of Seractil (Therabel Pharma, Milan, Italy) containing dexibuprofen (400 mg/tablet); one receiving two tablets/day of Seractil plus two tablets/day (10 am and 6 pm) of Tiobec 400 (Laborest, Milan, Italy) containing lipoic

acid, 400 mg/tablet; and one receiving two tablets/day of Seractil plus two tablets/day (10 am and 6 pm) of Lipicur (PharmExtracta, Pontenure, Italy) containing 400 mg lipoic acid plus 400 mg curcumin phytosome plus 4 mg piperine. All participants took the tablets on an empty stomach twice daily (before breakfast and dinner) for the whole length of the study (8 weeks). In agreement with Italian law (169/2004), Tiobec 400 and Lipicur were registered as food supplements with the Italian Minister of Health, with all their active ingredients belonging to the positive list of ingredients admitted as food supplements, and all their excipients being food-grade. All products, except dexibuprofen, were manufactured by SIIT (Milan, Italy). Lipoic acid and piperine were also provided by SIIT. Curcumin phytosome (also called Meriva) was provided by Indena, Milan, Italy. All the participants in the three groups were instructed to record the onset of any adverse events in a personal daily document, and specify their characteristics (severity, duration, and possible cause–effect relationship with drug administration), the number of missed tablets, and any changes in diet, physical exercise, or weight.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs (blood pressure and heart rate), a twelve-lead electrocardiogram, and the measurement of height and body weight. Fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were also analyzed. Liver function was evaluated through the measurement of transaminase, aspartate aminotransferase, and alanine aminotransferase. All participants were assessed for neuropathic pain according to a visual analog scale according to the original Scott–Huskisson scale,⁴² with scores from 0 (no pain) to 10 (unbearable pain). The health status of the participants was also assessed using the Short Form (36) Health Survey.^{42,43}

Safety measurements

Treatment tolerability was assessed through accurate interviews of the patients by the investigators and comparisons of clinical and laboratory values with baseline levels. Safety monitoring included physical examination, vital-sign assessment, weight, electrocardiogram, and adverse-event recording.

Statistical analysis

The statistical analysis used to evaluate the visual analog scale for pain was the between-within-subjects-design

analysis of variance. A multiple-comparison test (Tukey–Kramer test) was used⁴⁴ to analyze possible differences between the average values during the observation period. Values were considered significant at $P < 0.05$.

Results

This study was aimed at the investigation of an adjunctive therapy, added to the administration of an anti-inflammatory/analgesic drug and based on lipoic acid and curcumin, in patients with a diagnosis of lumbar sciatica, lumbar disc herniation and/or lumbar canal stenosis, or with carpal tunnel syndrome. In consideration of the well-known pharmacokinetic problems of curcumin, we assayed its clinical activity using a formula containing curcumin phytosome associated with piperine. The resulting product, Lipicur, also contained 400 mg lipoic acid. In order to be able to refer any possible clinical observations to the presence of curcumin alone, we also decided to assess the action of an add-on therapy based on lipoic acid. As shown in Tables 1 and 2, the personal characteristics (age and sex) of the individuals who completed the study (135 out of 141) demonstrate the absence of statistically significant differences in the three treatment groups.

As shown in Table 3, the scores of neuropathic pain in patients with a diagnosis of carpal tunnel syndrome were completely superimposable on enrollment. Treatment with dexibuprofen resulted in a progressive reduction of these score values. This reduction, however, measured after 4 and 8 weeks, was not statistically significant. Treatment with dexibuprofen and lipoic acid seems to lead to the same results. In this case, too, the decrease in score values relevant to neuropathic pain did not prove to be statistically significant. On the contrary, the situation of the individuals treated with the addition to dexibuprofen of curcumin and lipoic acid

Table 1 Age and sex of participants with a diagnosis of carpal tunnel syndrome

Treatment	Sex	n	Age* (years)	Age (M + F) [†] (years)
Dex	F	10	58.40 ± 9.86	61.07 ± 10.65
Dex	M	5	66.40 ± 11.19	
Dex + LA	F	9	64.67 ± 13.28	61.80 ± 15.11
Dex + LA	M	6	57.50 ± 17.90	
Dex + LA + CPP	F	10	59.10 ± 14.40	61.20 ± 13.88
Dex + LA + CPP	M	5	65.40 ± 13.22	

Notes: *Values are expressed as mean values ± standard deviation; [†]age (mean values ± standard deviation) of males (M) and females (F) of the same group.

Abbreviations: Dex, dexibuprofen; LA, lipoic acid; CPP, curcumin phytosome + piperine.

Table 2 Age and sex of participants with a diagnosis of lumbar sciatica

Treatment	Sex	n	Age* (years)	Age (M + F) [†] (years)
Dex	F	15	50.27 ± 12.80	50.80 ± 12.27
Dex	M	15	51.33 ± 1.56	
Dex + LA	F	14	51.93 ± 1.27	52.53 ± 15.50
Dex + LA	M	16	53.06 ± 7.65	
Dex + LA + CPP	F	15	53.07 ± 17.21	53.10 ± 16.27
Dex + LA + CPP	M	15	53.13 ± 15.87	

Notes: *Values are expressed as mean values ± standard deviation; †age (mean values ± standard deviation) of males (M) and females (F) of the same group.

Abbreviations: Dex, dexibuprofen; LA, lipoic acid; CPP, curcumin phytosome + piperine.

appears different. The score reduction at 4 weeks ($t = 4$) in this group is greater, albeit not statistically significant, than that observed in the other two treatment groups at the same assessment time. This difference became statistically significant after 8 treatment weeks, when the score reduced by 70% in comparison with $t = 0$, and by more than 50% in comparison with the measurements taken at $t = 8$ in the other two treatment groups.

The results shown in Table 3 seem to replicate those in Table 4, which describes the score trends in the individuals enrolled with a diagnosis of lumbar sciatica. Even in this case, the scores of neuropathic pain in the patients were totally superimposable. Treatment with dexibuprofen caused this score to reduce progressively. This reduction, however, measured after 4 and 8 weeks, was not statistically significant. Treatment with dexibuprofen and lipoic acid seems to lead to the same results. Even in this case, the decrease in the score values relevant to neuropathic pain were not found to be statistically significant. In the individuals treated with the addition to dexibuprofen of curcumin and lipoic acid, the score trends were instead much more marked. The score reduction at $t = 4$ (by over 50% in comparison with that at $t = 0$) was greater, albeit not to a statistically significant extent, than that observed in the other two treatment groups at

Table 3 Visual analog scale score* at $t = 0$ and after 4 and 8 weeks of treatment in participants with diagnosis of carpal tunnel syndrome

Treatment	n	Baseline	$t = 4$ weeks	$t = 8$ weeks
Dex	15	6.80 ± 1.52	5.73 ± 2.31	4.93 ± 2.58
Dex + LA	15	6.65 ± 1.39	5.40 ± 2.23	4.80 ± 2.21
Dex + LA + CPP	15	6.85 ± 1.48	4.13 ± 2.50	2.00 ± 2.14 [†]

Notes: *Values are expressed as mean values ± standard deviation; † $P < 0.05$ vs $t = 0$ of the same group and vs $t = 8$ of treatments with Dex or with Dex + LA.

Abbreviations: Dex, dexibuprofen; LA, lipoic acid; CPP, curcumin phytosome + piperine; vs, versus.

Table 4 Visual analog scale score* at $t = 0$ and after 4 and 8 treatment weeks in participants with a diagnosis of lumbar sciatica

Treatment	n	Baseline	$t = 4$ weeks	$t = 8$ weeks
Dex	30	6.87 ± 1.50	5.80 ± 1.90	4.60 ± 2.27
Dex + LA	30	6.81 ± 1.26	5.23 ± 1.79	4.47 ± 1.83
Dex + LA + CPP	30	6.91 ± 1.33	3.33 ± 2.62	2.17 ± 2.25 [†]

Notes: *Values are expressed as mean values ± standard deviation; † $P < 0.05$ vs $t = 0$ of the same group and vs $t = 8$ of treatments with Dex or with Dex + LA.

Abbreviations: Dex, dexibuprofen; LA, lipoic acid; CPP, curcumin phytosome + piperine; vs, versus; t, time.

the same assessment time. The difference became statistically significant after 8 treatment weeks, when the score decreased by approximately 70% in comparison with that at $t = 0$ and by more than 50% in comparison with the measurements taken at $t = 8$ in the other two treatment groups.

Table 5, concerning individuals with carpal tunnel syndrome, shows the number of weeks of treatment with dexibuprofen, which each individual was allowed to discontinue, in agreement with the clinicians, according to the trend of the neuropathic pain perceived. As the table shows, the individuals in the dexibuprofen group continued consuming the anti-inflammatory drug for almost the whole length of the study (about 7.5 weeks out of 8). A slightly lower value (about 6.7 weeks), but not differing significantly from that of the dexibuprofen group, was recorded for the individuals treated with dexibuprofen and lipoic acid. On the contrary, the addition to treatment with dexibuprofen of curcumin and lipoic acid reduced use of the anti-inflammatory drug by more than 3 weeks, in a statistically significant manner, in comparison with the dexibuprofen group.

Table 6 shows the number of weeks of treatment with dexibuprofen in individuals suffering from lumbar sciatica. The individuals of the dexibuprofen group resorted to the anti-inflammatory drug for almost the whole length of the study (approximately 7.2 out of 8 weeks). A slightly lower value (about 6.5 weeks), but not differing significantly from that of the dexibuprofen group, was recorded for the individuals

Table 5 Time (weeks)* before dexibuprofen discontinuation and gastralgia in participants with diagnosis of carpal tunnel syndrome

Treatment	n	Dex discontinuation	Gastralgia (n)
Dex	15	7.47 ± 1.41	3
Dex + LA	15	6.67 ± 1.95	5
Dex + LA + CPP	15	4.27 ± 1.03 [†]	2

Notes: *Values are expressed as mean values ± standard deviation; † $P < 0.05$ versus Dex.

Abbreviations: Dex, dexibuprofen; LA, lipoic acid; CPP, curcumin phytosome + piperine.

Table 6 Time (weeks)* before dexibuprofen discontinuation and gastralgia in participants with a diagnosis of lumbar sciatica

Treatment	n	Dex discontinuation	Gastralgia (n)
Dex	30	7.20 ± 1.63	9
Dex + LA	30	6.53 ± 1.96	6
Dex + LA + CPP	30	4.33 ± 1.92 [†]	6

Notes: *Values are expressed as mean values ± standard deviation; [†]P < 0.05 versus Dex.

Abbreviations: Dex, dexibuprofen; LA, lipoic acid; CPP, curcumin phytosome + piperine.

treated with dexibuprofen and lipoic acid. On the contrary, the addition to treatment with dexibuprofen of curcumin and lipoic acid reduced use of the anti-inflammatory drug by almost 3 weeks, in a statistically significant manner in comparison with the dexibuprofen group.

With regard to side effects, Tables 5 and 6 also show the number of individuals who complained of gastric discomfort like pain/heartburn in the stomach and/or esophagus with the need to resort to a gastroprotective drug. The differences are not statistically significant among the groups, but their trend seems to be related, at least in part, to the duration of the treatment with dexibuprofen. Even if the tables do not include all possible side effects, they were taken into consideration by the investigators. There did not seem to be any real correlation between these side effects (nausea, headache, insomnia, anxiety) and the treatments, nor were significant differences observed among the groups. Similar evidence of no differences was observed in terms of lipidic, glycemid, and hepatic assets among the different treatments (data not shown). The overall tolerability of the three treatments and compliance were very good, with the latter obviously being more favorable in the dexibuprofen group. The six individuals that were excluded from the statistical analysis had dropped out of the study on their own initiative for reasons not related to either tolerability or compliance.

Conclusion

Chronic low-back pain is the most common cause of long-term disability affecting middle-aged individuals, and about 80% of adults experience low-back pain episodes of variable degrees during a span of 1 year. As this disorder is resistant to drug therapy, patients are frequently compelled to undergo multidrug treatments. Although the incidence of carpal tunnel syndrome is not so high, the economic impact resulting from this type of disorder is of enormous importance, ranking among the highest expenditure items in terms of hospital health-care costs, as well as the costs associated with absenteeism and the burden of disability. Pharmacological treatment

(acetaminophen, tramadol, cyclooxygenase inhibitors, muscle relaxants, steroids, antidepressants, etc) and physical exercise (low-impact aerobics, McKenzie, Back School, etc) play an important role in the treatment of patients affected by these disorders.^{5,45} With regard to the drug therapy proposed to relieve the inconveniences of neuropathic syndromes, recent studies highlighted that therapeutic supplementation with alpha-lipoic acid reduces pain, dysesthesia, and numbness.⁴⁶ In this study, probably because of its brevity (8 weeks), lipoic acid, administered in association with dexibuprofen, did not demonstrate a real additive effect, at least in terms of pain reduction. On the contrary, when associated with curcumin, made available in turn by the phytosome vehicle and the presence of piperine, lipoic acid demonstrated an evident additive effect. As this study did not ascertain the clinical action of curcumin alone (in a phytosome form and with piperine), it was impossible to understand how much additive effect derived from the presence of bioavailable curcumin alone and how much derived from its association with lipoic acid. It is certain, however, that lipoic acid alone does not seem to have exerted an evident action, and this suggests that most of the reduction observed on the pain scale should be attributed to the anti-inflammatory, in part perhaps analgesic, effect of curcumin. The possibility that curcumin phytosome may determine a measurable analgesic effect has been hypothesized,³⁷ although in that case it was administered in higher doses. This clinical study obviously has some limitations that reduce the possibility of drawing definite conclusions. First of all, the absence of a group treated with dexibuprofen plus curcumin (complexed with phosphatidylcholine and with piperine) makes it impossible to exclude a priori any possible coaction determined by lipoic acid associated with curcumin and piperine. In addition, the absence of a double-blind procedure may have partly affected the results, since the participants in the study had free access to any test products and information, largely available and shared on the Internet. The small size of the sample, particularly in the assessment of the individuals with carpal tunnel syndrome (15 individuals per group), as well as the lack of multicentricity, also reduced the possibility of reaching more definite conclusions. Finally, the lack of follow-up information makes it impossible to draw valid conclusions with regard to diseases, where the assessment of the recurrence/relapse incidence and onset of long-term side effects appears to be extremely important. While giving all due consideration to the limitations arising from this study, it seems justified, however, to support the validity of a complementary approach to conventional therapy in individuals suffering from neuropathic pain through

such instruments as curcumin, if orally bioavailable, and its associations with alpha-lipoic acid.

Acknowledgment

The authors thank Martino Recchia for the statistical analysis.

Disclosure

FDP is the main formulator of the multi-ingredient formula Lipicur. The authors report no other conflicts of interest in this work.

References

- Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. *J Neurol Neurosurg Psychiatry*. 1997;62:310–318.
- England JD, Asbury AK. Peripheral neuropathy. *Lancet*. 2004;363:2151–2161.
- Merskey H, Bogduk N, editors. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle: IASP; 1994.
- Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630–1635.
- Govind J. Lumbar radicular pain. *Aust Fam Physician*. 2004;33:409–412.
- Younger DS. *Motor Disorders*. Philadelphia: Lippincott Williams & Wilkins; 2005.
- Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep*. 2009;13:185–190.
- Schnitzer TJ, Ferraro A, Hunsche E, Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. *J Pain Symptom Manage*. 2004;28:72–95.
- Kinkade S. Evaluation and treatment of acute low back pain. *Am Fam Physician*. 2007;75:1182–1188.
- Kovacs FM, Abaira V, Zamora J, Fernández C. The transition from acute to subacute and chronic low back pain: a study based on determinants of quality of life and prediction of chronic disability. *Spine (Phila Pa 1976)*. 2005;30:1786–1792.
- Freynhagen R, Baron R, Tölle T, et al. Screening of neuropathic pain components in patients with chronic back pain associated with nerve root compression: a prospective observational pilot study (MIPORT). *Curr Med Res Opin*. 2006;22:529–537.
- Heliövaara M, Mäkelä M, Knekt P, Impivaara O, Aromaa A. Determinants of sciatica and low-back pain. *Spine (Phila Pa 1976)*. 1991;16:608–614.
- Matsui H, Kanamori M, Ishihara H, Yudoh K, Naruse Y, Tsuji H. Familial predisposition for lumbar degenerative disc disease. A case-control study. *Spine (Phila Pa 1976)*. 1998;23:1029–1034.
- Simmons ED Jr, Guntupalli M, Kowalski JM, Braun F, Seidel T. Familial predisposition for degenerative disc disease. A case-control study. *Spine (Phila Pa 1976)*. 1996;21:1527–1529.
- Frymoyer JW. Lumbar disk disease: epidemiology. *Instr Course Lect*. 1992;41:217–223.
- Bland JD. Carpal tunnel syndrome. *BMJ*. 2007;335:343–346.
- Tanaka S, Wild DK, Seligman PJ, Behrens V, Cameron L, Putz-Anderson V. The US prevalence of self-reported carpal tunnel syndrome: 1988 National Health Interview Survey data. *Am J Public Health*. 1994;84:1846–1848.
- Palmer DH, Hanrahan LP. Social and economic costs of carpal tunnel surgery. *Instr Course Lect*. 1995;44:167–172.
- Hakim AJ, Cherkas L, El Zayat S, MacGregor AJ, Spector TD. The genetic contribution to carpal tunnel syndrome in women: a twin study. *Arthritis Rheum*. 2002;47:275–279.
- Bland JD. The relationship of obesity, age, and carpal tunnel syndrome: more complex than was thought? *Muscle Nerve*. 2005;32:527–532.
- Aroori S, Spence RA. Carpal tunnel syndrome. *Ulster Med J*. 2008;77:6–17.
- D'Arcy CA, McGee S. The rational clinical examination. Does this patient have carpal tunnel syndrome? *JAMA*. 2000;283:3110–3117.
- Attal N, Cruccu G, Hanpää M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*. 2006;13:1153–1169.
- Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132:237–251.
- Vo T, Rice AS, Dworkin RH. Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use? *Pain*. 2009;143:169–171.
- Schnitzer TJ. Update on guidelines for the treatment of chronic musculoskeletal pain. *Clin Rheumatol*. 2006;25 Suppl 1:S22–S29.
- Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain*. 1999;83:389–400.
- Ziegler D. Treatment of diabetic neuropathy and neuropathic pain. How far have we come? *Diabetes Care*. 2008;31 Suppl 2:S255–S261.
- Memeo A, Loiero M. Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study. *Clin Drug Investig*. 2008;28:495–500.
- Ziegler D, Hanefeld M, Ruhnau KJ, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care*. 1999;22:1296–1301.
- Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha lipoic acid: a meta-analysis. *Diabet Med*. 2004;21:114–121.
- Ziegler D. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review. *Treat Endocrinol*. 2004;3:173–189.
- Ammon HPT, Wahal MA. Pharmacology of *Curcuma longa*. *Planta Med*. 1991;57:1–7.
- Funk JL, Oyarzo JN, Frye JB, et al. Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. *J Nat Prod*. 2006;69:351–355.
- Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. *Life Sci*. 2006;78:2081–2087.
- Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4:807–818.
- Di Pierro F, Rapacioli G, Di Maio EA, Appendino G, Franceschi F, Togni S. Comparative evaluation of the pain-relieving properties of a lecithinized formulation of curcumin (Meriva), nimesulide, and acetaminophen. *J Pain Res*. 2013;6:201–205.
- Steigerwalt R, Nebbioso M, Appendino G, et al. Meriva, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy. *Panminerva Med*. 2012;54:11–16.
- Mazzolani F. Pilot study of oral administration of a curcumin-phospholipid formulation for treatment of central serous chorioretinopathy. *Clin Ophthalmol*. 2012;6:801–806.
- Appendino G, Belcaro G, Cornelli U, et al. Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. *Panminerva Med*. 2011;53:43–49.
- Rinwa P, Kumar A, Garg S. Suppression of neuroinflammatory and apoptotic signaling cascade by curcumin alone and in combination with piperine in rat model of olfactory bulbectomy induced depression. *PLoS One*. 2013;8(4):e61052.

42. Mansourian M, Mahdiyeh Z, Park JJ, Haghjooyeivanmard S. Skew-symmetric random effect models with application to a preventive cohort study: improving outcomes in low back pain patients. *Int J Prev Med*. 2013;4:279–285.
43. Lopes A, Frade IC, Teixeira L, Almeida M, Dias L, Henriques AC. Quality of life assessment in a living donor kidney transplantation program: evaluation of recipients and donors. *Transplant Proc*. 2013;45:1106–1109.
44. Kirk, RE. *Experimental Design: Procedures for the Behavioral Sciences*. Pacific Grove (CA): Brooks/Cole; 1982.
45. Patrick LE, Altmeyer EM, Found EM. Long-term outcomes in multidisciplinary treatment of chronic low back pain: results of a 13-year follow-up. *Spine (Phila Pa 1976)*. 2004;29:850–855.
46. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care*. 2006;29:2365–2370.

Journal of Pain Research

Publish your work in this journal

The Journal of Pain Research is an international, peer-reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication.

Submit your manuscript here: <http://www.dovepress.com/journal-of-pain-research-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.