Effects of a nutraceutical combination in patients with chronic lumbosacral radicular pain

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Summary

Drugs used for the treatment of chronic lumbosacral radicular pain (LRP) may have frequent adverse effects leading to medication withdrawal. The use of add-on nutraceuticals, which have no side effects, may therefore play a role in LRP treatment.
We performed a six-week, single-center, open label prospective uncontrolled clinical study to evaluate the effect of a nutraceutical combination (Noxiall®) used as an add-on therapy in patients with chronic LRP. Fifteen patients were treated with Noxiall® twice a day for 10 consecutive days, followed by once-daily administration up to the end of the six-week treatment. The participants were evaluated at two visits (before-after), when primary and secondary outcomes were assessed. We found a significant reduction in pain severity post-treatment, as assessed using a numerical rating scale (p= 0.03), and a significant reduction in painkiller intake (p=0.03). Nutraceuticals could be a complementary therapy for chronic LRP.

KEY WORDS: low back pain, neuropathic pain, pain management.

Introduction

Lumbosacral radicular pain (LRP) is described as pain radiating from the back and buttocks to the legs in a dermatomal distribution without neurological signs (Allegri et al., 2016). The estimated annual prevalence of LRP ranges from 9.9 to 25% in the general population (Konstantinou and Dunn, 2008). The wide variation of prevalence may be attributed to its uncertain definition, differences in data collection methods and populations studied, and the different time frames of reported prevalence (Konstantinou and Dunn, 2008).
In 70% of cases, LRP completely or partially disappears within three months, but 30% of patients still report LRP after three months and in these cases the condition is defined chronic LRP (Weber, 1993, Benoist, 2002). Low back pain is the principal cause of disability worldwide and a major socio-economic problem (Balagué et al., 2012).
Chronic LRP may be produced by mechanical compression of the nerve root (mechanical neuropathic pain), by damage to nociceptive sprouts within a degenerated disc (local neuropathic pain), or by the action of inflammatory mediators produced by a degenerative disc (Freynhagen and Baron, 2009; Cohen and Mao, 2014). Radicular lesions may be also present, and result in sensory and motor symptoms and signs and reduced deep tendon reflexes (Tarulli and Raynor, 2007).

The goals of neuropathic pain management are to identify the underlying cause, remove risk factors, decrease pain, preserve function and avoid future exacerbation. The condition demands a multimodal management plan (Dworkin et al., 2013, Finnerup et al., 2015) that includes the use of medications (Baron et al., 2016) along with non-pharmacological approaches (i.e. physical therapy modalities, rehabilitation techniques and psychosocial/behavioural interventions) (Akyuz and Kenis, 2014; Castelnuovo et al., 2016). A variety of drugs, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants, opioids and topical treatments, are routinely recommended (Vogt et al., 2005) and may be effective, to varying degrees, in chronic LRP (Baron et al., 2016). However, many patients frequently report incomplete pain relief or severe side effects that may result in treatment withdrawal (Baron et al., 2016).

Nutraceuticals or dietary supplements can be used as adjunct therapies in patients with pain (Halsted et al., 2003). Noxiall® is available in Italy as a dietary supplement (Italian Registry of Supplements code 88326). It is composed of four natural agents with demonstrated anti-inflammatory and analgesic activity in animal models and patients, i.e., palmitoylethanolamide, myrrh, β-caryophyllene and Rosmarinus officinalis (Dolara et al., 1996, Katsuyama et al., 2013, Di Cesare Mannelli et al., 2016; Gabrielsson et al., 2016). This nutraceutical combination, being devoid of side effects, might be helpful in the treatment of chronic LRP. To date, no published clinical studies have explored the potential role of a nutraceutical combination in the treatment of chronic LRP. Therefore, an open-label prospective evaluation was performed to examine the effectiveness and side effect profile of the abovementioned nutraceutical combination in patients with chronic LRP.

Materials and methods

Patients

Patients with chronic LRP (i.e., pain lasting more than 3 months; Treede et al., 2015) were enrolled from the outpatient Neurology Section at the University of Verona, Italy. Neuropathic pain was diagnosed according to clinical and instrumental criteria (Treede et al., 2008; Finnerup et al., 2016) and the Italian version of the Douleur Neuropathique en 4 Questions (DN4) questionnaire (cutoff ≥ 4) (Bouhassira et al., 2005, Ciaramitaro et al., 2017).

The inclusion criteria were: (1) age 18 years or over; (2) daily pain, persisting for at least 3 months from diagnosis; (3) moderate-to-severe pain intensity, corresponding to a 0-10 Numerical Rating Scale (NRS) score of 4 or over; (4) LRP of neuropathic origin (see above); (5) normal cognitive and language abilities, as judged by performance in compiling a background questionnaire and answering clinical interview questions; (6) provision of written informed consent.

The exclusion criteria were: (1) peripheral mono- or polyneuropathy; (2) pregnancy; (3) lower limb pain or sensory symptoms secondary to osteoarthritis or peripheral vascular diseases; (4) depression and/or dementia; (5) treatment with antidepressants or anticonvulsants; (6) spinal fracture. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients signed the informed consent form and the study had local ethics committee approval.

Study design

This was an open-label, single center, prospective, uncontrolled, observational study. The treatment duration was six weeks. Patients began therapy with Noxiall®, twice a day, for 10 consecutive days, followed by dose escalation to once a day through to the end of the 6-week period of treatment. Patients were allowed to continue using their regular painkillers, whose dosage remained constant throughout the study.

The participants were evaluated at two visits. During the first visit, patients were assessed for inclusion/exclusion criteria, baseline demographics and clinical characteristics, pain descriptors and outcome measures. Patients were given detailed instructions on administration of the nutraceutical therapy. At the second visit, at the end of the 6 weeks of nutraceutical intake, outcome measures were reassessed, and side effect profiles were evaluated. During the treatment, an experimenter phoned the patients once weekly to support compliance, and took note of any complaint or side effect reported.

Outcome measures

The assessment protocol included primary and secondary outcome measures.

The primary outcome was the 0-10 NRS, a valid and reliable 11-point verbal rating scale commonly used to evaluate pain in clinical practice (Williamson and Hoggart, 2005).

The secondary outcomes were: a) the amount of concomitant painkiller treatment, defined as the number of days of painkiller intake during the previous week; b) the Oswestry Disability Index (ODI); c) tactile, pain and tolerance thresholds; d) the Patient's Global Impression of Change (PGIC); and e) side effects during treatment.

The ODI is a condition-specific and validated outcome measure of functional status and pain-related disability. Its 10 items explore pain intensity, the ability to care for oneself (washing, dressing, etc.), the ability to lift objects, walk, sit and stand, sleeping, sexual function, social life and travelling.

A score from 0 to 20% denotes a condition of minimal disability (the patient can deal with most daily life activities). A score from 21 to 40% denotes moderate disability (the patient has difficulty sitting, lifting objects and remaining standing, and has limitations in terms of travelling, social life and some vocational activities). A score from 41 to 60% denotes severe disability (i.e., most activities of daily living are compromised). Patients with a score from 61% to 80% have a level of disability affecting all aspects of the patient's daily life. Finally, a score ranging from 81 to 100% indicates a bedridden patient (Fairbank et al., 1980).

Tactile, pain and tolerance thresholds were assessed with the subject lying comfortably on a bed in a quiet room with an ambient temperature of 20-23° C. The electrical stimulus consisted of a 0.2 ms square-wave electrical pulse delivered to the big toe of the affected and unaffected leg through Ag-AgCl ring electrodes applied to the skin surface. The anode was located 1.5 cm distally to the cathode. The thresholds were established with the method of limits. Electrical stimuli of increasing intensity were consecutively delivered to the big toe on the affected side, beginning with the lowest stimulation intensity (0.5 mA) and gradually increasing this, by 0.5 mA steps, until the subjects perceived the electrical stimulus (tactile threshold). The intensity of the electrical stimulus was further increased by 0.5 mA steps until they reported a change in sensation from not painful to "slightly painful" (pain threshold). Finally, the intensity of the electrical stimulus was progressively increased further, by 1 mA steps, until the patient described a sensation of "intolerable" pain (pain tolerance threshold; Zambito Marsala et al., 2011).

The PGIC was used to quantify the patients' overall impressions of the post-treatment change in their condition, evaluating this in terms of activity restrictions, symptoms, emotions and quality of life. This instrument consists of seven sentences, scored with a minimum score of 1 (no change, or condition has got worse) to a maximum score of 7 (a great deal better, considerable improvement; Hurst and Bolton, 2004).

Statistical analysis

Statistical analyses were carried out using the IBM® SPSS® statistical package, version 20.0 for Macintosh. Descriptive statistics included frequency tables and calculation of means and standard deviations.

Normal distribution was checked using the Shapiro-Wilk test. Parametric (t-test, paired sample) or non-parametric (Wilcoxon's signed-rank test) tests were applied accordingly.

The single imputation (simple mean) method was used to handle missing data. $P < 0.05$ (two-tailed) was taken as the significance level for all the tests.

Results

Fifteen patients with chronic LRP were recruited during the study period. One patient began the study but was unable to participate further and dropped out after the first visit. Demographic and clinical characteristics of the patients (9 women, mean age: 55.1 ± 14.4 years, mean disease duration: 3.9 ± 2.1 years; 5 men, mean age: 49 ± 17.6 years, disease duration: 3.2 ± 1.9 years) are reported in Table I. All the patients had a lumbar disc herniation as confirmed by MRI.

The lumbar disc herniation was at L5-S1 level in 11 patients, and at L4-L5 level in the others. According to the dermatome map (Van Boxem et al., 2010), pain was right sided extending from L1 to L5 in five patients, left sided extending from L1 to L5 in seven patients, and bilateral, from L1 to L5 in two patients.

The mean daily pain duration was 18.36 ± 7.97 hours. As regards the pain descriptors, numbness and hypoesthesia to touch were very common, being reported in 14 patients. The other descriptors consisted of pins and needles (n=7), burning (n=7), painful cold sensation (n=6), electric shock sensation (n=6), tingling (n=6), hypoesthesia to prick (n=5), brushing sensation (n=4) and itching (n=1).

The baseline NRS score was 6.53 ± 1.85. Eleven patients were under painkiller treatment (frequency of intake = 3.73 ± 3.06 days/week), which resulted in consistent but not completely satisfactory pain reduction (n = 4), partial pain reduction (n = 4), or no effect (n = 3). Patients reported the use of one or more of the following painkillers: acetaminophen, NSAIDs, opioids, corticosteroids, ketoprofen and cortisone. Spine X-ray excluded major structural changes.

Outcomes

Primary outcome

We found a significant reduction in the NRS score after treatment (p= 0.03), with a mean pre- vs post-treatment difference of 1.66 points (Table II, Figure 1).

Secondary outcomes

We found a significant reduction in painkiller intake (p=0.03), with a mean pre- vs post-treatment difference of 1.46 days/week (Table II, Figure 2). There were no significant post-treatment changes in the other secondary outcome measures. No patient experienced side effects. In most patients the pain (NRS) score change corresponded to an improvement of their condition, also rated as “better” on the PGIC (Hurst and Bolton, 2004).

Table I - Baseline clinical characteristics of patients with chronic lumbosacral radicular pain (n = 14).

Patient	Age	Sex	Disease duration (y)	Affected side	Disc herniation	Pain duration (daily hours)	Pain distribution (dermatomes)	NRS	Types of painkiller
1	38	M	4	Right	L5-S1	24	Right L4-L5	6	Acetaminophen, NSAIDs
2	58	F	3	Left	L5-S1	7	Left L4, L5, S1	8	Acetaminophen, NSAIDs
3	37	M	1	Left	L5-S1	24	Left L1 – L5	9	Opioids
4	46	F	3	Left	L5-S1	6	Left L1 – L5	8	-
5	77	M	3	Right	L5-S1	24	Right L1 – L5	6	-
6	78	F	1	Left	L5-S1	24	Left L1 – L3	5	Acetaminophen, NSAIDs, opioids
7	57	F	6	Right	L5-S1	24	Right L1 – L5	8	Acetaminophen, opioids, corticosteroids
8	37	M	2	Left	L4-L5	24	Left L1 – L5	5	Corticosteroids
9	38	F	5	Left	L5-S1	12	Left L1 – L5	5	Corticosteroids
10	63	F	4	Left	L5-S1	24	Left L1 – L5	9	Acetaminophen, opioids
11	54	F	5	Right	L4-L5	7	Right L1 – L5	5	NSAIDs, corticosteroids
12	33	F	7	Right	L4-L5	24	Right L1 – L5	9	-
13	69	F	1	Right	L5-S1	9	Bilateral L1 – L5	4	Ketoprofen
14	56	M	6	Left	L5-S1	24	Bilateral L1 – L5	4	Cortisone

Abbreviations: M=male; F=female; NRS=Numerical Rating Scale; NSAIDs=non-steroidal anti-inflammatory drugs.

Table II - Comparison of outcomes and psychophysical procedures after 6 weeks of treatment with a nutraceutical combination.

	Before treatment Mean (SD)	After treatment Mean (SD)	P-Value
Numerical Rating Scale score	6.53 (1.85)	4.87 (2.61)	.03*
Painkiller intake (number of days during previous week)	3.73 (3.06)	2.27 (2.76)	.03*
Oswestry Disability Index (%)	31.80 (13.74)	29.33 (15.31)	n.s.
Tactile threshold (mA)			
Affected side	6.58 (1.78)	6.23 (2.45)	n.s.
Non-affected side	6.16 (2.16)	5.87 (1.83)	n.s.
Pain threshold (mA)			
Affected side	25.37 (7.45)	23.09 (5.57)	n.s.
Non-affected side	23.90 (8.66)	23.97 (5.96)	n.s.
Pain tolerance (mA)			
Affected side	36.17 (12.19)	34.84 (14)	n.s.
Non-affected side	34.54 (15.30)	36.02 (15.18)	n.s.
Patient's Global Impression of Change -	-	2.91 (2.02)	

Abbreviations: SD=standard deviation; n.s.=not significant

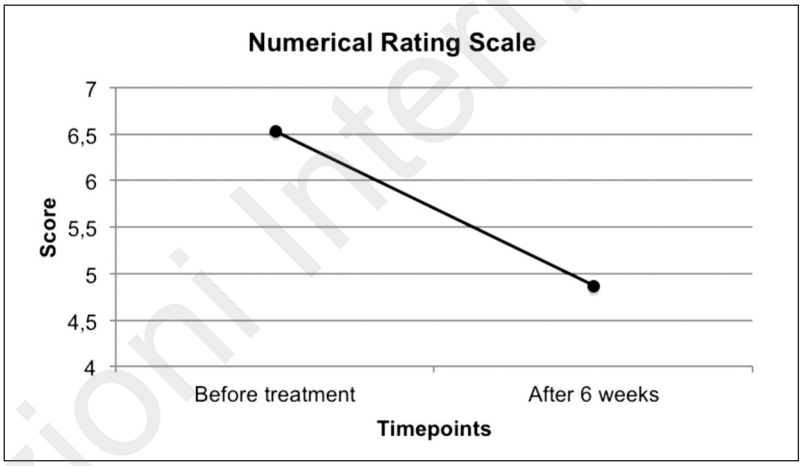

Fig. 1 - Changes in the Numerical Rating Scale (NRS) score for chronic lumbosacral radicular pain over the assessment period.
The NRS scores significantly decreased from 6.53 prior to treatment to 4.87 (p=.03) after 6 weeks of treatment.

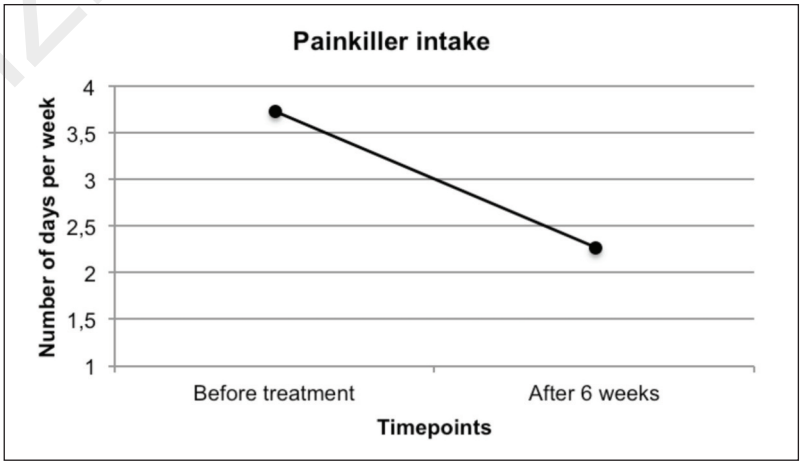

Fig. 2 - Changes in painkiller intake over the assessment period.
The number of days with painkiller intake in the previous week decreased from 3.73 prior to treatment to 2.27 (p=.03) after 6 weeks of treatment.

Discussion

The results of this open-label prospective trial offer preliminary evidence that a combination of nutraceuticals (Noxiall®) could play a role as an adjunct therapy in the treatment of chronic LRP. After a six-week treatment, the patients recorded a significant 1.66-point reduction in their NRS score and a significant reduction in painkiller intake. Although the ODI showed an only non-significant improvement after treatment, some patients reported being better able to cope with some activities of daily living. Overall, the PGIC results showed they felt their condition to be "better" after than before the treatment. Finally, we did not find significant changes in tactile, pain and tolerance thresholds.

To date, no other data are available on this specific nutraceutical combination, used as an adjunct therapy for the treatment of chronic LRP. The current standard pharmacological treatments for this condition include acetaminophen, NSAIDs, antidepressants, anticonvulsants, opioids and topical therapies (Baron et al., 2016), but these painkillers often result in incomplete pain relief and/or side effects. Moreover, it is important that these patients receive personalized pain treatment, given the remarkable variability in terms of type of pain (i.e., neuropathic and/or nociceptive), severity of symptoms, comorbidity (e.g. sleep disorders or depression), adverse effects and drug interactions (Baron et al., 2016). Therefore, satisfactory pain relief can necessitate the use of several drugs with different mechanisms and sites of action (Cohen and Mao, 2014).

The term 'nutraceutical' is a combination of the words 'nutrition' and 'pharmaceutical' and was first defined as a food (or part of a food) that offers medical or health benefits, including prevention and/or treatment of a disease (Kalra, 2003). Nutraceuticals or dietary supplements, deriving from plants and marine organisms, can be valid adjunct therapies (Halsted et al., 2003). Experimental data suggest that Noxiall®, thanks to the action of its components, might reduce pain through modulation of inflammation and pain.
Palmitoylethanolamide is an endogenous fatty acid that has been used for the treatment of chronic pain for several years (Gabrielsson et al., 2016). It has been reported to act on the cannabinoid system which modulates microglia and mast cells and inhibits the release of proinflammatory mediators. β-caryophyllene selectively binds to type 2 cannabinoid receptors (CB2) acting as an agonist at the neuronal microglia and reducing pain (Katsuyama et al., 2013). Myrrh can exert analgesic, anaesthetic, anti-microbial and anti-inflammatory properties through two bioactive sesquiterpenes (Dolara et al., 1996). Finally, carnosic acid and carnosol are two phenolic diterpenes obtained from Rosmarinus officinalis, which have antioxidant and neuroprotective effects and effects on nociception and sensory processing (Di Cesare Mannelli et al., 2016).

The major limitations of this preliminary study are the small sample size and the design. Without a placebo comparator, our findings should be seen as preliminary results that need to be confirmed in a randomized, double-blind, placebo-controlled study. Nonetheless, we found a NRS score reduction of close to 2 points, which is considered moderately clinically meaningful (Farrar et al., 2001). It has been suggested that different neuropathic pain descriptors might reveal different underlying pain mechanisms. Future studies should investigate whether Noxiall® may be active on specific sensory profiles of neuropathic pain.

References

Akyuz G, Kenis O (2014). Physical therapy modalities and rehabilitation techniques in the management of neuropathic pain. Am J Phys Med Rehabil 93: 253-259.

Allegri M, Montella S, Salici F, et al (2016). Mechanisms of low back pain: a guide for diagnosis and therapy. Version 2. F1000Res. 5.

Balagué F, Mannion AF, Pellisé F, et al (2012). Non-specific low back pain. Lancet 379:482-491.

Baron R, Binder A, Attal N, et al. (2016). Neuropathic low back pain in clinical practice. Eur J Pain 20: 861-873.

Benoist M (2002). The natural history of lumbar disc herniation and radiculopathy. Joint Bone Spine 69: 155-160.

Bouhassira D, Attal N, Alchaar H, et al (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 114: 29-36.

Castelnuovo G, Giusti EM, Manzoni GM, et al (2016). Psychological treatments and psychotherapies in the neurorehabilitation of pain: evidences and recommendations from the Italian Consensus Conference on pain in neurorehabilitation. Front Psychol 19: 115.

Ciaramitaro P, Padua L, Devigili G, et al (2017). Neuropathic pain special interest group of the Italian Neurological Society. Prevalence of neuropathic pain in patients with traumatic brachial plexus injury: a multicenter prospective hospital-based study. Pain Med 18: 2428-2432.

Cohen SP, Mao J (2014). Neuropathic pain: mechanisms and their clinical implications. BMJ 348: f7656.

Di Cesare Mannelli L, Micheli L, Maresca M, et al (2016). Anti-neuropathic effects of rosmarinus officinalis L. terpenoid fraction: relevance of nicotinic receptors. Sci Rep 6: 34832.

Dolara P, Luceri C, Ghelardini C, et al (1996). Analgesic effects of myrrh. Nature 379: 29.

Dworkin RH, O'Connor AB, Kent J, et al (2013). International Association for the Study of Pain Neuropathic Pain Special Interest Group. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 154: 2249-2261.

Fairbank JC, Couper J, Davies JB, et al (1980). The Oswestry low back pain disability questionnaire. Physiotherapy 66: 271-273.

Farrar JT, Young JP Jr, LaMoreaux L, et al (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94: 149-158.

Finnerup NB, Attal N, Haroutounian S, et al (2015). Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 14: 162-173.

Finnerup NB, Haroutounian S, Kamerman P, et al (2016). Neuropathic pain: an updated grading system for research and clinical practice. Pain 157: 1599-1606.

Freynhagen R, Baron R (2009). The evaluation of neuropathic components in low back pain. Curr Pain Headache Rep 13: 185-190.

Gabrielsson L, Mattsson S, Fowler CJ (2016). Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol 82: 932-942.

Halsted CH (2003). Dietary supplements and functional foods: 2 sides of a coin? Am J Clin Nutr 77: 1001S-1007S.

Hurst H, Bolton J (2004). Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 27: 26-35.

Kalra EK (2003). Nutraceutical-definition and introduction. AAPS PharmSci 5: E25.

Katsuyama S, Mizoguchi H, Kuwahata H, et al (2013). Involvement of peripheral cannabinoid and opioid receptors in β-caryophyllene-induced antinociception. Eur J Pain 17: 664-675.
Konstantinou K, Dunn KM (2008). Sciatica: review of epidemiological studies and prevalence estimates. Spine (Phila Pa 1976) 33: 2464-2472.
Tarulli AW, Raynor EM (2007). Lumbosacral radiculopathy. Neurol Clin 25: 387-405.
Treede RD, Rief W, Barke A, et al (2015). A classification of chronic pain for ICD-11. Pain 156: 1003-1007.
Treede RD, Jensen TS, Campbell JN, et al (2008). Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 70: 1630-1635.
Van Boxem K, Cheng J, Patijn J, et al (2010). Lumbosacral radicular pain. Pain Pract 10: 339-358.
Vogt MT, Kwoh CK, Cope DK, et al (2005). Analgesic usage for low back pain: impact on health care costs and service use. Spine (Phila Pa 1976) 30: 1075-1081.
Weber H, Holme I, Amlie E (1993). The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. Spine (Phila Pa 1976) 18: 1433-1438.
Williamson A, Hoggart B (2005). Pain: a review of three commonly used pain rating scales. J Clin Nurs 14: 798-804.
Zambito Marsala S, Tinazzi M, Vitaliani R, et al (2011). Spontaneous pain, pain threshold, and pain tolerance in Parkinson's disease. J Neurol 258: 627-633.