Neuroreflexotherapy for non-specific low-back pain (Review)

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[Intervention Review]

Neuroreflexotherapy for non-specific low-back pain

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ABSTRACT

Background

Among the wide range of therapeutic alternatives proposed for the management of low-back pain (LBP), a less widely used technique from Spain, called neuroreflexotherapy (NRT) has claimed to show very favourable results, mainly in patients with chronic low-back pain.

Objectives

To assess the effectiveness of NRT for the treatment of non-specific LBP in adult patients, aged 16 to 65 years. A secondary objective was to compare NRT with other conventional interventions.

Search strategy

In February 2008, we updated the searches in CENTRAL (Issue 1, 2008), MEDLINE and EMBASE. No new trials were identified.

Selection criteria

Only randomised controlled trials (RCTs) of NRT for the treatment of patients with a clinical diagnosis of non-specific LBP were included.

Data collection and analysis

Two authors independently selected trials and extracted data using pre-designed forms. Because the outcome variables were not assessed in a homogenous way, it was not possible to pool the results to obtain an estimate of global effect, as initially planned.

Main results

Three RCTs were included, with a total of 125 subjects randomised to the control groups and 148 subjects receiving active NRT. Neuroreflexotherapy was the same in all three trials, while the control groups received sham-NRT in two trials and standard care in one. Two trials studied patients with chronic LBP, the third studied patients with a mix of chronic and sub-acute LBP. Clinical outcomes were measured in the short-term (15 to 60 days) in all three trials; in one trial, resource utilization was measured after one year. Individuals who received active NRT showed statistically significantly better outcomes than the control groups for measures of

pain, degree of mobility, disability, medication use, consumption of resources and costs. No significant differences were observed for quality of life measures. Side effects were more frequently reported in the control groups during short-term follow-up, with no major side effects reported by those receiving active NRT.

Authors' conclusions

NRT appears to be a safe and effective intervention for the treatment of chronic non-specific LBP. The efficacy is less clear for sub-acute LBP. However, these results are limited to three trials conducted by a small number of specifically trained and experienced clinicians, in a limited geographical location. No data are available on the ease and time-frame needed to achieve that level of expertise. RCTs by other practitioners, in other locations, that replicate the effects reported in this review are needed before recommending a broader practice.

PLAIN LANGUAGE SUMMARY

Neuroreflexotherapy for non-specific low-back pain

Neuroreflexotherapy, provided in specialized clinics in Spain, appears to reduce pain and disability for patients with chronic non-specific low-back pain.

Clinicians use a wide range of treatments to manage chronic low back pain. There is often little scientific support that they work, or that they would be useful for a broader population. In this review, neuroreflexotherapy performed better than placebo or standard care. However, until research duplicates these results in different settings, there is no strong evidence that it will work as well outside the specialty clinics in Spain.

BACKGROUND

A large variety of therapeutic interventions are available for the treatment of chronic low-back pain (LBP). However, the effectiveness of most of these interventions (educational, ergonomic or therapeutic) has not been convincingly demonstrated (Deyo 1996; Kaplansky 1998; van Tulder 1997a; van Tulder 2000) and consequently, the therapeutic management of chronic LBP varies widely.

Among the wide range of treatments proposed, a less widely used technique from Spain, called neuroreflexotherapy (NRT) has claimed very favourable results in the management of LBP. Neuroreflexotherapy is characterised by temporary implantation of a number of epidermal devices into trigger points in the back and into referred tender points in the ear. The theoretical physiological basis of this procedure has been outlined in depth in a number of publications (Kovacs 1993; Kovacs 1997; Kovacs 2002). Staples are implanted superficially into the skin, to a depth of less than two millimetres. No problems with pain or scarring associated with the procedure are reported in the literature. Neuroreflexotherapy is performed without anaesthesia and takes about 60 minutes for the implantation. The staples remain in place for up to 90 days in the back and up to 20 days in the ear. Neuroreflexotherapy may be confused with acupuncture as both use puncture devices, but, according to the first author of the studies (personal communication), different zones of the skin are being stimulated. Acupuncture for LBP has been the subject of several systematic reviews, including a Cochrane review (Van Tulder 1999), but none have included NRT trials.

A large follow-up study in 2751 patients (Moreno 1992) and several clinical trials on NRT (Kovacs 1993; Kovacs 1997; Kovacs 2002) claiming surprisingly consistent, favourable results attracted our attention and stimulated our interest in a review of the possible effectiveness of this procedure.

OBJECTIVES

The aim of this review was to systematically assess the effectiveness of NRT for the treatment of non-specific LBP in adult patients, focusing on those of working age.

The principal objective of this review was to validly and reliably answer the questions:

- Is NRT effective for adult patients suffering from non-specific LBP?
- Is NRT safe in terms of the rate of adverse events, for the treatment of such patients?

The secondary objective was to compare NRT with other conservative interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs), published in any language, were sought for this review.
Trials were included by consensus after independent assessments by two authors (GU and AM), according to the following general criteria:
a) RCTs and CCTs should have an appropriate control group: placebo for the principal objective and any other conventional intervention for the secondary objective.
b) For the principal comparison, RCTs and CCTs should be blinded for patients and outcome assessors.

Types of participants

Adult subjects of working age (16 to 65 years old) with non-specific LBP that was not relieved with conservative treatment.
Patients with (sub)acute LBP (2 to 12 weeks) and/or chronic LBP (more than 12 weeks) were included.
All subjects with organically-caused back disorders (such as infection, metastatic diseases, neoplasm, osteoporosis, rheumatoid arthritis or fractures) were excluded, but imaging studies were not required to rule out organicity.

Types of interventions

Neuroreflexotherapy (defined as temporary implantation of epidermal devices into trigger points at the site of each subject's clinically involved dermatomes on the back and into referred tender points in the ear) was the therapy of interest. Acupuncture techniques were excluded from this review, since NRT and acupuncture are ostensibly (and probably actually) different procedures and there is already a Cochrane review on the latter (Van Tulder 1999).
For the primary objective, we considered placebo or sham treatment to be appropriate when the patients were given an intervention that did not penetrate the skin, or were given simulated treatment (the intervention was applied in purportedly non-reflexogenous areas or in reflexogenous areas that did not correspond with the involved lumbar dermatomes). Other conservative interventions were considered for comparisons for the secondary objective.

Types of outcome measures

RCTs and CCTs that used at least one of the five primary outcome measures that we considered to be the most important were included:
a) Pain intensity.
b) A global measure of well-being or quality of life.
c) A global measure of disability for daily activities.
d) Functional ability.
e) Return to work (days off work).
Other secondary outcome measures for this review were:
f) Medication use.
g) Costs.
h) Side effects.
These outcomes should have been measured and recorded before randomisation or before the start of the intervention (baseline) and again after the intervention period in order to assess change over time (up to three months for very short-term assessment, between three and six months for short/medium term assessment, and longer than six months for longer-term assessment).

Search methods for identification of studies

For the electronic search, we combined parts A and B of the Cochrane Back Group search strategy (van Tulder 1997) and our specific search strategy for NRT.
See Appendix 1 for the specific search for neuroreflexotherapy in MEDLINE (Ovid).
The specific search for neuroreflexotherapy was changed accordingly to search EMBASE (Ovid). See Appendix 2.
Relevant RCTs and CCTs meeting the inclusion criteria for this review were identified in the following steps:
(A) A computer-aided search of the MEDLINE (1966-2002) and EMBASE (1988-2002) databases using the search strategy recommended by the Editorial Board of the Cochrane Back Review Group (van Tulder 1997a).
(B) Screening of references in relevant reviews and in RCTs and CCTs identified in step A.
(C) Screening of the Cochrane Central Register of Controlled Trials, which is included in The Cochrane Library Issue 3, 2002.
(D) Personal communication with content experts in the field.
All articles were coded and details of source, intervention and population recorded. The author compiling the references (GU) decided on potentially relevant trials and sent a full copy of them to the other authors (AM and KB) for inclusion assessment.

Data collection and analysis

1. Study selection.

Two authors (GU and AM) searched The Cochrane Library, MEDLINE, and EMBASE and decided on potentially relevant trials. They independently reviewed potential articles and decided

final eligibility according to the pre-determined selection criteria. One of the authors was a content-expert in the area (AM), while the other was not (GU). There was full agreement between them. Two other authors (KB and GZ) also read the full text of the articles, and concurred with the opinions of the first two authors.
Due to the low number of papers and the easily recognisable characteristics of the technique, the assessment of eligibility criteria, data extraction and quality assessment could not be performed in a blinded fashion.

2. Methodological quality assessment.

The methodological quality of each article was independently assessed by three authors (GU, AM and KB) using the criteria list recommended by the Cochrane Back Review Group (van Tulder 1997a). Only the 10 items reflecting the internal validity of the RCTs were used. Equal weights were applied to all criteria. There was agreement among the three assessors.

3. Data extraction.

A specific form was designed and used by two authors (GU and AM) to independently extract relevant outcome data and descriptive information on the study population and the interventions from each trial. The third author (KB) checked the extraction, making minor corrections.
The first author of the three included trials was contacted by GU to obtain more detailed information on scarring of the skin after the procedure, the number of sub-acute patients included in the first trial and additional details on the NRT technique.

4. Data analysis.

For similar comparisons and outcome measures, we had planned to calculate an overall relative risk using the Mantel-Haenszel method for dichotomous outcomes, and weighted mean differences (or standardised mean differences if different instruments of measure were used) for continuous outcomes, using a fixed effect model or a random effects model (in case statistically significant heterogeneity was detected). We had also planned to perform a sensitivity analysis, using only the highest quality studies, in order to assess whether this dimension played a role in the results being observed. As the outcome measures used in the trials were clinically too heterogeneous, we performed a qualitative analysis, with a special emphasis on the methodological quality of the trials and the consistency of their findings. Sub-group analyses (sub-acute and chronic LBP) were not performed as data were not provided separately for these patients.

RESULTS

Description of studies

See: Characteristics of included studies.
Only three RCTs, including 273 patients, fulfilling the inclusion criteria were electronically identified: Kovacs 1993; Kovacs 1997 and Kovacs 2002. The characteristics of these studies are described in the *Table of Characteristics of Included Studies* and Table 1; Table 2 and Table 3. All three trials were conducted by the same primary investigator, albeit with different research teams. Kovacs 1993 and Kovacs 1997 compared NRT with a placebo (sham intervention), which was given in the same way in both studies, matching the number of devices between experimental and control patients. The only difference between the two groups was the location of the epidermal devices, which in the control group were implanted within a 5 cm radius of the target zones. The burins fell out spontaneously (between 5 and 17 days) and the staples were left in place until they were removed at the end of the follow-up period (30 and 45 days in Kovacs 1993 and Kovacs 1997, respectively). Kovacs 2002 compared NRT with standard care, described as counseling, drug treatment, possible laboratory tests, and imaging studies, potential referral to physiotherapy, rehabilitation for further treatment or to specialists for further evaluation.

Table 1. Results (Kovacs 1993)

Outcome	Description	Categories/Measures	NRT	Sham	P
Spontaneous pain relief	T30-T0 (self reported)	Disappeared + greatly improved / slightly improved + unchanged + worsened	45/2	1/41	<0.0001

Table 1. Results (Kovacs 1993) (*Continued*)

Referred pain relief	T30-T0 (self reported)	Disappeared + greatly improved / slightly improved + unchanged + worsened	36/0	0/31	<0.0001
Tenderness pain relief	T30-T0 (self reported)	Disappeared + greatly improved / slightly improved + unchanged + worsened	46/1	0/42	<0.0001
Daily activity	T30-T0 (self reported)	Normal + greatly improved / slightly improved + unchanged + worse	36/5	1/36	<0.0001
Functional status	T30-T0 (physical exam)	Normal + greatly improved / slightly improved + unchanged + worse	45/2	1/42	<0.0001
Changes in medication use	T30-T0 (self reported)	Suspended + reduced / maintained + increased	44/3	11/32	<0.0001
No. days off work	Self reported	Mean (SD)	4.70 (11.60)	12.50 (13.24)	<0.003
No. days in bed	Self reported	Mean (SD)	0.96 (4.92)	5.21 (9.50)	<0.008
Side effects	Spontaneously self-reported	Yes / No	4/43	17/26	<0.002

Table 2. Results (Kovacs 1997)

Outcome	**Description**	**Categories/Measures**	**NRT**	**Sham**	**P**
Spontaneous pain relief	T45-T0 (VAS)	Mean difference (SD)	+3.09 (2.56)	+0.34 (2.98)	<0.001
Referred pain relief	T45-T0 (VAS)	Mean difference (SD)	+2.03 (2.49)	-0.61 (4.17)	0.003

Table 2. Results (Kovacs 1997) (*Continued*)

Pain on movement relief	T45-T0 (VAS)	Mean difference (SD)	+2.87 (3.01)	+0.03 (3.50)	<0.001
Anterior flexion	T45-T0 (VAS)	Mean difference (SD)	+2.53 (3.07)	-0.09 (3.86)	0.033
Flexion to the right	T45-T0 (VAS)	Mean difference (SD)	+2.28 (3.20)	-0.09 (4.16)	0.012
Flexion to the left	T45-T0 (VAS)	Mean difference (SD)	+2.25 (2.79)	+0.14 (3.76)	0.012
Bending forward	T45-T0 (physical exam)	Mean difference (SD)	-0.82 (10.56)	-5.38 (12.42)	0.096
Effect of LBP on quality of life: daily activities	T45-T0 (COOP chart)	Mean difference (SD)	+0.81 (1.35)	+0.61 (1.38)	0.534
Effect of LBP on quality of life: social activities	T45-T0 (COOP chart)	Mean difference (SD)	+0.26 (1.39)	+0.08 (1.50)	0.594
Effects of LBP on quality of life: pain during the past 6 weeks	T45-T0 (COOP chart)	Mean difference (SD)	+1.13 (1.46)	+0.56 (1.18)	0.067
Effects of LBP on quality of life: change in condition	T45-T0 (COOP chart)	Mean difference (SD)	+2.45 (1.11)	+2.83 (0.85)	0.095
Effects of LBP on quality of life: overall health	T45-T0 (COOP chart)	Mean difference (SD)	+0.44 (0.89)	+0.25 (0.87)	0.340
Effects of LBP on quality of live: overall quality of life	T45-T0 (COOP chart)	Mean difference (SD)	+0.16 (0.97)	+0.28 (0.85)	0.542
Physical condition	T45-T0 (COOP chart)	Mean difference (SD)	+0.27 (1.26)	+0.44 (1.23)	0.164
Side effects	Spontaneously self-reported	Yes/No	7/41	5/37	NS

Table 3. Results (Kovacs 2002)

Outcome	Description	Measures	Control	NRT	P
Improvement in LBP (VAS)	T60-T0 (self reported)	Median (range)	1.92 (-1.25, 3.04)	5.50 (3.73, 8.80)	0.000
Improvement in referred pain (VAS)	T60-T0 (self reported)	Median (range)	0.58 (-1.50, 2.01)	3.63 (2.69, 7.30)	0.001
Improvement in disability (Roland Morris Questionnaire)	T60-T0 (self reported)	Median (range)	2.05 (-1.50, 6.67)	8.67 (2.00, 13.33)	0.007
Improvement in quality of life (EuroQuol)	T60-T0 (self reported)	Median (range)	-14.61 (-18.83, 22.50)	-11.67 (-50.00, -3.33)	0.628
Sick leave (days)	1 year (applicable for workforce people only)	Median (range)	105.2 (5, 330)	3.2 (0, 32.5)	0.001

In Kovacs 1993 and Kovacs 2002, patients were recruited from primary care consultations. In Kovacs 1997, they were recruited from the outpatient departments of three rheumatology services and one rehabilitation service of three hospitals. Patients with symptomatic spinal stenosis, clinically noticeable progressive motor weakness or sphincter impairment suggesting cauda equina syndrome were excluded. Kovacs 2002 used a cluster randomisation procedure, in which physicians (n = 21) rather than patients (n = 104) were selected as units of randomisation and analyses.

This review only considered the evaluation at the end of the follow-up periods to be of major clinical importance. This varied from 30 days (Kovacs 1993) to 45 days (Kovacs 1997) to 60 days (Kovacs 2002). This third trial also recorded resource utilization at one year. Since it was not feasible to blind the therapists, the outcome assessors were blinded to treatment allocation. In Kovacs 2002, the clinical outcome variables were evaluated by self-administered questionnaires (or telephone interviews) for the final outcome, whilst additional data were obtained by the family physicians, who were not blinded to the treatment allocation.

Risk of bias in included studies

The methodological quality of the three included trials is shown in detail in Table 4. There was no disagreement between the authors. A third author (KB) concurred with the opinions of the first two authors (GU and AM). The first two trials received a score of nine out of a possible ten, suggesting that appropriate measures had been put in place to minimise bias, unlike the last trial that only scored three out of a possible ten.

Table 4. Criteria for the Risk of Bias Assessment

Criteria for a judgment of yes for the sources of risk of bias
Method of randomisation adequate: A random (unpredictable assignment sequence. Examples of adequate methods are computer generated random number table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alteration should not be regarded as appropriate.
Concealment of treatment allocation: Assignment generated by an independent person not responsible for determining the eligibility of the patients; this person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.
Blinding of patients: The reviewer determines if there was enough information about the blinding of the patient to score a yes.
Blinding of care providers:The reviewer determines if there was enough information about the blinding of the care provider to score a yes.
Blinding of outcome assessors: The reviewer determines if there was enough information about the blinding of the outcome assessors to score a yes.
Drop-out rate described and acceptable: The number of participants who were included in the study but did not complete the observation period or were not included int eh analysis must be described and reasons given. If the percentage of drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias, a yes is scored. (NB: these percentages are arbitrary, not supported by literature)
Similarity of baseline characteristics: In order to receive a yes, groups have to be similar at baseline regarding demographic factors, duration and severity of complaints and value of main outcome measure(s).
Co-interventions avoided or similar: Co-interventions should either be avoided in the trial design or comparable between the index and control groups.
Compliance acceptable: The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention(s) and control intervention(s).
Timing outcome assessments similar: Timing of outcome assessment be identical for all intervention groups and for all important outcome assessments.

In Kovacs 1993 and Kovacs 1997, patients were allowed to continue their previously prescribed pharmacological treatment, and consumption of drugs was measured in both groups (type and amount) before the intervention and at the end of the follow-up period. In Kovacs 1993, there were a few unexplained missing values, more in the control than in the treatment group. Only patients analysed at the end of the follow-up were considered for the analysis of each variable. If missing values were equated to therapeutic failures in the analysis, this would have favoured the experimental (NRT) group. In Kovacs 1993, a Chi squared test was performed for all comparisons using categorical variables.

Kovacs 2002 randomised physicians rather than patients and this randomisation was concealed. Neither patients nor care providers were blinded to the intervention and both groups of patients were free to continue with the local standard protocol for the management of LBP. The evolution was determined by the comparison of the value of the variables at the first and last assessments. Therefore, any missing value at any of the two assessments impeded such a comparison. There were missing values due to dropouts and exclusions (five patients), but there were some additional unexplained missing values in both groups. Although the paper only reports data from valid cases, results for the principal outcomes (improvement in pain and disability) were re-analysed by the authors of the original research, at our request, according to the intention to treat principle. The assumption made in this later analysis was

that missing values were equivalent to no effect and were therefore assigned the same value as in the baseline.

Effects of interventions

Study Selection

Although a very limited number of trials on NRT were expected a priori because of the local use of this technique, we nevertheless conducted a full literature search. The Cochrane Library (Issue 3, 2002) identified 99 potential references, the MEDLINE search (1966-2002) identified 91, and the EMBASE search (1988-2002) 38.

After screening titles, abstracts and keywords, both authors (GU and AM) considered only three studies to be potentially eligible. Reviewing the full articles of these three studies, in collaboration with a third author (KB), confirmed their eligibility. None of the other identified studies evaluated NRT as defined for this review, although some used a similar term (reflex-therapy) referring to interventions such as manipulations, neural therapy and acupuncture.

Kovacs 1993 included patients from primary care, with a minimum of seven days of LBP, however, the mean duration of pain was 84 weeks and 73 weeks for experimental and control groups respectively. Kovacs 1997 included patients from rheumatology and rehabilitative services, with a minimum of twelve weeks of LBP -- the mean duration of LBP was 63 weeks in the control group and 86 in the experimental group. Kovacs 2002 included patients from primary care, with a minimum of two weeks duration of LBP -- the mean duration of LBP was 48.13 days and 17.5 days for experimental and control groups respectively.

The literature search was updated in MEDLINE and EMBASE on November 5, 2004. No new trials on the effectiveness of NRT were identified, but there was a case report by Conde-Salazar that described a patient with a personal history of metal intolerance, who developed contact dermatitis, secondary to the insertion of the staples (Conde-Salazar 2004).

The literature search was updated in MEDLINE and EMBASE from 2004 to February, 2008 and in CENTRAL from 2002 to 2008 (Issue 1, 2008). The results were combined and the duplicates removed, leaving 324 unique references. There were no new reports of trials of the effectiveness of neuroreflexotherapy as a treatment intervention for LBP.

Effectiveness of Neuroreflexotherapy

A) Neuroreflexology versus sham Neuroreflexology.

Our search identified two RCTs comparing NRT to a sham intervention. It was not possible to conduct subgroup analyses for patients with sub-acute and chronic LBP because Kovacs 1993 only presented aggregated results.

Since none of the outcome variables were assessed in a homogenous way, it was not possible to aggregate the results to obtain an estimate of global effect. Results of each outcome for each RCT are presented in Table 1; Table 2 and Table 3.

In this review, only the "residual benefit", measured in Kovacs 1993, was considered to be of major clinical interest, with the "maximum beneficial effect" discarded as a transitory outcome. In Kovacs 1997, all patients underwent two separate evaluations at each follow-up assessments (the trial provides the score of each assessor but not an average of both assessments). As the concordance between these two assessors was very high, only the score obtained by the first of the two assessors was considered in this review for practical reasons.

A.1) Pain relief:

Both studies showed a statistically significant reduction in the severity of pain, whether local or referred, in the experimental group, at the end of the follow-up period (30 and 45 days, respectively). In Kovacs 1993, whereas almost all the patients in the NRT group (45 among 47) reported major relief or the disappearance of the pain, almost no-one in the control group (1 among 42) showed a similar improvement. In Kovacs 1997, the change in pain shows a large difference in favour of NRT. In this latter study, the observed size of the reduction in the follow-up assessment immediately after the intervention was 60% in the experimental group, but dropped to 50% when measured 45 days later. In the control group, an improvement of 20% was detected just after the procedure and dropped to 10% 45 days later. Similar results were observed in the evaluation of "pain on pressure" (Kovacs 1993), "pain on movement" (forward flexion) and "pain experienced in the last six weeks" (Kovacs 1997).

A.2) A global measure of well-being or quality of life:

This measure was only assessed in Kovacs 1997, using the COOP chart. This is an instrument developed by The Dartmouth Primary Care Cooperative Information Project that assesses general dimensions of quality of life rather than the influence of any particular illness (Nelson 1987), and has been validated in Spanish. For the three dimensions related to perceived health or quality of life (from among a total of seven assessed with this instrument) a small favourable result was only detected for "Change in quality of life". The differences found for the variables "overall health" and "overall quality of life" were not significant.

A.3) A global measure of disability for daily activities:

In Kovacs 1993, the observed improvement in the ability to perform daily activities, measured 30 days after the intervention using the COOP chart, was highly significant in the NRT group, with 88% of patients reporting a substantial improvement, whereas only three per cent of the control group showed this degree of improvement. In Kovacs 1997, there was no significant difference between the two groups in their ability to perform activities of daily living.

A.4) Functional ability:

In Kovacs 1993, patient's "functional ability" at day 30 showed a significant improvement in the experimental group (96% of the patients), while only 2.3% of patients in the control group reported a significant improvement.

Kovacs 1997 evaluated the ability of the patients to bend forwards (fingertip-to-floor distance) as part of the physical examination (measurements were repeated three times and in each case the shortest distance was recorded). A greater and statistically significant improvement was seen in the experimental group at 45 days.

A.5) Return to work:

During the follow-up period, the mean numbers of days off work due to an episode of LBP in the experimental group in Kovacs 1993 was one third of that in the control group (4.7 versus 12.5 days) and statistically significant. The number of days off work were similar at baseline in both groups.

A.6) Medication use:

Both trials recorded medication consumption for pain, as reported by the patients. At the last assessment in Kovacs 1993, 94% of patients in the experimental group reported that they had suspended or decreased the use of drugs , while this percentage was only 26% in the control group. This difference was not observed in Kovacs 1997, where patient's consumption of drugs at baseline was sparse in both groups.

A.7) Side effects:

In Kovacs 1993, patients were asked about adverse affects occurring during the follow-up period. These were more frequent in the control group (65% versus 9%), due mainly to gastric discomfort secondary to NSAID consumption, while local discomfort due to skin tautness caused by the devices in the hours following their implant, were reported equally (same percentage) in both groups. According to the original articles, none of these side effects were important enough to require the early extraction of the epidermal devices.

Pain involved in attaching the staples was not specifically reported in the trials, but seemingly no patient refused the intervention. No information is reported in the trials on scarring from the staples. According to the lead author who was contacted by the authors, skin scarring is not a relevant problem as staples are implanted very superficially in the skin and most scars disappear within one month.

A.8) Other outcomes:

The average number of days spent "lying in bed" in Kovacs 1993 was one day for the intervention group and five days for the control group. This difference was statistically significant. There were no significant differences noted in Kovacs 1997 for physical condition or social activities.

B) Neuroreflexology versus Standard Care.

Kovacs 2002 examined a mixture of sub-acute and chronic patients, with pain lasting two or more weeks. All the outcomes related to effectiveness were assessed using specific scales at the initial visit and at two subsequent obligatory visits (at day 15 and 60). There was an additional follow-up assessment at day 354, when patients were interviewed by telephone regarding any treatment or diagnostic tests that had been prescribed since the last visit to the primary care centre. Data on duration of sick leave due to LBP were obtained from the register of the National Institute of the Social Security. For all clinical outcomes, the final ratings (day 60) were subtracted from those obtained in the first visit. Thus, effectiveness was determined by the variation of the median scores of the groups of patients who had received neuroreflexotherapy and those who had not. Between-group comparison were performed using practices rather than patients as the units of analysis, using a non-parametric test. So, the outcome variables measuring effectiveness were averaged over all patients per physician.

B.1) Pain relief:

A statistically significant reduction in the severity of pain was reported in the experimental groups at the end of the follow-up period (at 60 days), although there was an improvement in both experimental and control groups (median: NRT 5.50 [range 3.73 to 8.80] vs Control 1.92 [range -1.25 to 3.04]; $p < 0{,}000$). For referred pain, the medians were NRT 3.63 [range 2.69 to 7.30] vs. Control 0.58 [range -1.50 to 2.01]; $p < 0.001$).

B.2) Disability:

There was a statistically significant improvement in disability at the end of the follow-up period (at 60 days) reported by those who had received NRT (median: NRT 8.67 [range 2.00 to 13.33] vs Control 2.05 [range -1.50 to 6.67]; $p < 0.007$).

B.3) Quality of life:

The trial measured quality of life by the self-administered EuroQol questionnaire (using the validated Spanish version). Although all groups tended to report some improvement in their quality of life, there was no statistically significant difference at the end of the follow-up period (at 60 days) between those who had received NRT and those who had not.

B.4) Sick leave:

Information regarding the number of days on sick leave during the one-year follow-up period was obtained for all patients from the register of the National Institute of the Social Security. Patients in the experimental groups experienced a statistically significantly shorter duration of sick leave (median 3.2 days; range 0 to 32.5) compared to the control groups (median 105.2 days; range 5 to 330).

B.5) Consumption of resources during follow-up:

During the one-year follow-up period, participating physicians recorded the use of health care services resulting from the management of LBP. Patients in the experimental groups showed statistically significantly fewer visits to private and public specialists, fewer radiographic studies prescribed in the primary care setting, and a lower cost of drug treatment.

B.6) Side effects:

Patients were asked about adverse affects occurring during the follow up period. Two patients in the control groups reported epigastralgia and treatment with nonsteroidal anti-inflammatory drugs had to be withdrawn. Side effects related to NRT (such as transient tightness, skin irritation, and infection of the skin secondary to implantation of the surgical material) were not reported during the trial.

B.7) Cost-effectiveness:

The trial included a cost-effectiveness analysis in which the cost per point of improvement on the corresponding scale was used as a measure of efficiency. They conducted sensitivity analyses according to three specific assumptions: a) the most optimistic, b) the most conservative and c) the average assumption. In all cases, cost-effectiveness ratios for pain and disability where reported to be favourable for the experimental group.

DISCUSSION

Neuroreflexotherapy is unusual in that it seems to be currently performed in a limited geographical region (Spain), by a relatively small number of practitioners. Furthermore, the same principal investigator (who is also a leading NRT practitioner) was involved in all of the published RCTs. Nevertheless, those facts are not an a priori barrier to a review of the effectiveness of the therapy, if suitable published trials are available for analysis.

Overall Results

A) Neuroreflexology versus sham Neuroreflexology.

The reported results from the two published randomised trials comparing NRT with sham-NRT show a statistically significant short-term positive effect on chronic back pain for the main outcomes of pain, ability to perform daily activities, and functional ability, as well as secondary outcomes of return to work, side effects and medication use, when the treatment was given by a very limited number of particularly experienced physicians (a total number of two in these trials). Although the follow-up period in both trials (30 and 45 days) is not sufficient to assess the effect of NRT on recurrence of back pain, it can be considered adequate for assessing the effect of the intervention during the current episode. The effect appeared to be rapid and remained for at least six weeks after intervention in most of patients treated.

In spite of differences in the reduction of pain and disability between the treated group and the control group, there were no substantial differences reported in their quality of life or perceived health as measured by instruments which are not specific for low-back pain.

The extent of the reported clinical advantage of NRT over sham treatment is unusually high compared with other trials of treatment for back pain. A surprising lack of improvement was seen in any of the outcome measures for the patients in the control groups. A possible explanation is that the instrument used in Kovacs 1993 (categorical outcomes) was sensitive to the level of change in the intervention group but not the seemingly smaller changes in the control group. In Kovacs 1997, the data tables in the original study do show improvements in the control group, though these are very small and much less than the intervention group. Bearing in mind the short follow-up and the fact that these were chronic pain patients, it is conceivable that this could represent the 'placebo' response for this type of patient.

A limitation of these trials is that one might normally expect a longer follow-up for what is a somewhat invasive procedure, but it is the authors' impression from the published papers that NRT is not an aggressive procedure likely to have long-term detrimental consequences.

Blinding of patients is a crucial issue in trials on LBP interventions. Kovacs 1993 did not provide detailed information on this. Nevertheless, the information given in both original papers suggests that intervention and control groups were handled in the same fashion, and it is said that the number and general location of staples/burins was largely matched between experimental and control groups. So, taking into account the high level of (reported) similarity between real and sham NRT, it is doubtful that the patients could detect real from sham unless they had specialist knowledge of the NRT procedure.

B) Neuroreflexology versus Standard Care.

The results from one recent randomised trial of NRT as a supplement to standard management protocol for LBP in routine general practice show a statistically significant short-term (60-days) effect on pain relief (local and referred) and ability to perform daily activities, and for duration of sick leave and consumption of resources throughout the one-year follow-up period. Again, in spite of differences in the reduction of pain and disability between the treated and control groups, there was no difference reported in their quality of life as measured by instruments that are not specific for low-back pain.

There is some concern about the reliability of the one-year assessment of consumption of resources by means of a telephone call, as recall bias may have occurred. Nevertheless, the difference be-

tween groups, as well as the sensitivity analysis performed by the authors, suggests that NRT reduces to some extent the cost of the management of LBP compared with standard care.

The imbalances observed between groups at baseline is a potential problem with cluster randomisation. Nevertheless, these differences do not invalidate the general conclusions of the trial, as they suggest a worse prognosis in patients in the intervention group, which is against the hypothesis demonstrated in the study.

The extent of the reported changes in the short-term (60 days) for clinical outcomes, and reduced sick leave and lower health-care costs over a 12-month period, suggest that NRT can be an effective and safe supplement to the standard primary care management protocol for LBP in Spain.

POTENTIAL FOR SELECTION BIAS:

We identified only three published RCTs of NRT, all of them completed in Spain. However, this is a technique that is (confidently) believed to be used in a limited geographical area only, so we believe our search strategy had a low potential for study-selection bias.

METHODOLOGICAL QUALITY:

The methodological quality of the RCTs included in this review was reasonably high. All of the RCTs seemed to satisfactorily meet the essential methodological criteria related to randomisation, concealment of allocation, and blinding of the response assessment; we did not identify obvious reasons to suspect bias with regard to these issues. With respect to losses and dropouts, there are some doubts, because not all patients randomised were accounted for in the analysis of each variable. However, in view of the apparent effect size, imputing missing values as failures would be unlikely to affect the conclusions in this instance.

AUTHORS' CONCLUSIONS

Implications for practice

The main finding of this review is that NRT appears to be a safe and effective intervention for the short-term treatment of chronic non-specific LBP. That said, it is important to add some caveats. These results are currently limited to trials conducted only in one country, by a small number of specially trained practitioners. This makes it difficult to recommend the wider use of NRT without first conducting randomised controlled trials by other practitioners, in other countries.

There are no objective reasons to suppose that socio-demographic, biological or cultural variables could affect the overall effects on pain and functional status. However, psychosocial factors may influence the degree of disability and the rate of return to work, and therefore results on these variables may vary from one setting to another.

Implications for research

Generalisation of the results remains difficult to establish, partly because of the very limited number of clinicians involved in the published trials, and partly because the results may only be valid when highly trained physicians are performing the interventions. No data are available on the ease and time-frame needed to achieve that level of expertise. Therefore, if further RCTs are undertaken in other settings, it is fundamental to assess the degree of competence that therapists would need to reach in order to achieve similar results to those observed in these trials.

Effectiveness of NRT in patients with (sub)acute LBP has not been clearly demonstrated. A well designed RCT with larger samples and precise patient selection criteria is needed to answer this question.

It needs to be determined if the unusually positive results in the current trials can be replicated. These trials would ideally, but not necessarily, be multi-centered and multinational, with the involvement of different clinical teams not previously linked to the authors of the original studies. That would also allow a better estimation of both the efficacy and effectiveness of NRT.

ACKNOWLEDGEMENTS

We would like to thank Dr. Maurits van Tulder for his advice while writing the protocol for the review. We also want to thank the first author of the three existing trials on NRT (Dr. FM Kovacs) for providing more detailed information than that previously published.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Kovacs 1993

Methods	Allocation to the study groups was established according to a table of random permutations. Sealed opaque envelopes with correlative Arabic numerals on the front contained the corresponding number of the table. Both the outcome assessor and patients were unaware of the group where patients had been assigned.
Participants	91 adult patients (20 to 65 years old) presenting an episode of LBP refractory to conventional medical treatment lasting for more than 7 days consecutively recruited from primary care consultations in Palma de Mallorca (Spain). Both groups were fully comparable for all the main variables. Mean duration of the current episode = 18 months. Mean duration of LBP syndrome for all the participants = 8 years.
Interventions	Patients in the treatment group received a single NRT intervention. Patients in the control group underwent a similar procedure although inappropriate zones were stimulated (sham intervention). Two therapists treated patients. Patients in both groups were allowed to continue drug and physiotherapy treatments as prescribed by their GPs.
Outcomes	1) Measures of change with respect the baseline (Day 30-Day 0): a) Pain relief, b) Daily activity, c) Medication use, d) Degree of mobility. 2) Others as number of days off work, number of days laying in bed, side effects.
Notes	Results at the baseline (before the intervention), immediately after intervention (at 15 minutes) and at short term (30 days) are provided.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes - patients?	Yes	
Blinding? All outcomes - providers?	No	

Kovacs 1993 (*Continued*)

Blinding? All outcomes - outcome assessors?	Yes	
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	drop-outs - less than 20%
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	Yes	patients were allowed to continue pre-trial meds if needed
Compliance acceptable?	Yes	
Timing outcome assessments similar?	Yes	

Kovacs 1997

Methods	Randomization was carried out according to a table of random permutations. Only the person responsible for randomising patients and the therapist knew the result of the assignment. Both the outcome assessors and patients were unaware of the group where patients had been assigned.
Participants	78 adult patients (27 to 65 years old) presenting an episode of LBP refractory to conventional treatment lasting for more than 12 weeks consecutively recruited from outpatient clinics at the hospital level in Madrid (Spain). Both groups were fully comparable for all the main variables. Mean duration of the current episode = 63 and 86 weeks. Mean duration of LBP syndrome = 8,9 and 9,2 years.
Interventions	Patients in the treatment group received a single NRT intervention. Patients in the control group underwent a similar procedure although inappropriate zones were stimulated (sham intervention). The same therapist treated all patients. Patients in both groups were allowed to continue drug and physiotherapy treatments as prescribed by their GPs.
Outcomes	1) Measures of change with respect the baseline (Day 45-Day 0): a) Pain relief, b) Daily activity, c) Medication use, d) Degree of mobility. 2) Others as number of days off work, number of days laying in bed, side effects.
Notes	Results at the baseline (before the intervention), immediately after intervention (at 5 minutes) and at short term (45 days) are provided.

Risk of bias

Item	**Authors' judgement**	**Description**

Kovacs 1997 (*Continued*)

Adequate sequence generation?	Yes	
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes - patients?	Yes	
Blinding? All outcomes - providers?	No	
Blinding? All outcomes - outcome assessors?	Yes	
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	less than 20%
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	Yes	patients were allowed to continue pre-trial meds if needed
Compliance acceptable?	Yes	
Timing outcome assessments similar?	Yes	

Kovacs 2002

Methods	Cluster randomisation (21 voluntary GPs were randomised). Each doctor recruited a median of 2.5 (Control) and 3 patients (NRT group) (range 1 to 14).
Participants	104 adult patients (28 to 61) presenting an episode of LBP lasting at least 14 days in spite of conventional treatment were consecutively recruited from primary care consultations in Palma de Mallorca (Spain). Intensity of pain and duration of current episode were higher in the NRT group while length of time on sick leave before inclusion was slightly higher in the control group. Median duration of the current episode of LBP = 17.5 days (Control) and 48.13 (NRT group). About 90% in the NRT group and 82% in the control group had experienced one or more previous episodes.
Interventions	Patients in the treatment group received NRT intervention (mean number of procedures 1.44) in addition to the standard care for LBP in the primary care setting. Patients in the control group received the so-called standard protocol for LBP.

Outcomes	1) Measures of change with respect the baseline (Day 60-Day 0): a) Pain relief (local and referred), b) Disability, c) Quality of life, and d) Side effects. 2) Measures at the end of 1-year follow-up period: a) number of days off work, b) consumption of resources.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	No	As physicians in this study were randomized not to treat with A versus B, but to refer patients or not to refer patients to a specialized unit on Neuroreflexotherapy, we believe that in this particular case the risk of selection bias was low.
Blinding? All outcomes - patients?	No	not applicable
Blinding? All outcomes - providers?	No	not applicable
Blinding? All outcomes - outcome assessors?	No	not applicable
Incomplete outcome data addressed? All outcomes - drop-outs?	No	
Similarity of baseline characteristics?	No	
Co-interventions avoided or similar?	Yes	Patients were allowed to continue pretrial meds if needed
Compliance acceptable?	Unclear	Unclear from text
Timing outcome assessments similar?	Yes	

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

1.SURGICAL-STAPLING$.SH
2.SURGICAL-STAPLERS$. SH
3.PROSTHESIS-IMPLANTATION. SH
4.PROSTHESES-AND-IMPLANTS.SH
5.IMPLANTS-EXPERIMENTAL$.SH
6.SKIN.SH
7.EPIDERMIS.SH
8.EAR$.SH
9.REFLEXOTHERAPY$.SH
10.PHYSICAL-STIMULATION.SH
11.NEUROREFLEXOTHERAP$
12.NEURO-REFLEXOTHERAP$
13.or/1-12

Appendix 2. EMBASE search strategy

1. NEUROREFLEXOTHERAP*
2. explode "NERVE-STIMULATION"/ all subheadings
3. #1 OR #2

WHAT'S NEW

Last assessed as up-to-date: 31 January 2008.

3 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 2, 2004

1 February 2008	New search has been performed	In February 2008, we updated the searches in CENTRAL (Issue 1, 2008), MEDLINE and EMBASE. No new trials were identified.
1 November 2004	New search has been performed	The literature search was updated in MEDLINE and EMBASE in November 2004. No new trials on the effectiveness of NRT were identified, but there was a case report by Conde-Salazar that described a case of contact dermatitis in an individual with a personal history of metal intolerance, secondary to the insertion of the staples. This information has been added to the review.

CONTRIBUTIONS OF AUTHORS

GU and AM independently applied the selection criteria, assessed the quality of included trials and extracted the data.

KB and GZ independently read the trials and gave advise on the opinion of the two reviewers regarding the selection criteria, quality assessment and interpretation of results.

GU and KB wrote the draft of the review.

XB gave external advice in the process of the review.

DECLARATIONS OF INTEREST

None of the authors have any experience in performing NRT, have not participated in any of the trials included in this review, nor have any kind of professional involvement with the investigators or clinics in the trials reviewed. The authors undertook the task for its scientific and clinical interest only. The author who initially registered the title (GU), although not working in this field, chose this topic mainly because of the impact of this procedure on the Spanish social mass media. Since then, GU has kept relatively close contact with Dr. Kovacs in relation to this and other initiatives (a grant application). One author (GZ) visited one NRT clinic in Palma de Mallorca in April 2002, whilst another (KB) has worked with the lead author of the trials on an unrelated initiative.

NOTES

Note from the Co-Editors. This review addresses all of the following comments in their discussion, however, the Co-editors wish to echo the unusual nature of the evidence available to date . The effect of Neuroreflexotherapy is studied in three RCTs with 273 patients with low-back pain. Dr. Kovacs was the principal investigator for all three trials, albeit with different research teams. Patients in the trials were recruited from primary care settings and treated in three Kovacs Foundation clinics (A Spanish private, non-profit research and medical institution). This association does not imply methodologically flawed trials. In fact, the review was clear that the trials complied with the Back Group's methodological standards.

However, we would feel more reassured if similar evidence was available from RCTs conducted in other countries, with other care providers and different researchers. The very large positive response in the intervention group compared to the placebo group is unusual for trials in chronic back pain. Duplication of these results in other settings would also enable better assessment of the generalizability of these findings.

Therefore, we concur that until research duplicates these results in different settings, there is no strong evidence that it will work as well outside the specialty clinics in Spain.