OPEN ACCESS Freely available online

Journal of Pain Management & Medicine

Research Article

Effetiveness of Duloxetine on Pain and Quality of Life in Chronic Back Pain in Patients who had Posterior Spinal Fixation (PSF)

Arezoo Samadi[1*], Razieh Salehian[2], Danial Kiani[3] and Atefeh Ghanbari Jolfaei[4]

[1]*Psychiatrist, Fellowship of Psychosomatic Medicine, Iran*
[2]*Assistant professor of Psychiatry, Department of psychiatry, Rasoul-e Akram Hospital, Iran University of Medical Science, Iran*
[3]*Resident of Neurosurgery, Rasoul-e Akram Hospital, Iran University of Medical Science, Iran*
[4]*Associate professor of psychiatry, Minimally Invasive Surgery Research Center, Iran University of Medical Science, Iran*

ABSTRACT

Background: Low back pain is a common disorder with high disability in physical and mental health. The prevalence of low back pain is about 84% and in chronic cases (more than 3 months)is about 23%.For treatment pharmacological, nonpharmacological and surgery are common. In this study we want to search the effectiveness of Duloxetine on pain and quality of life in patients with chronic low back pain who had posterior spinal fixation.

Methods: In this randomized, placebo-controlled trial done in 6 months 50 patients who had CLBP and were candidated for PSF surgery selected and divided in 2 groups (drug and placebo).

Results: Significant differences were evidenced among groups for Visual Analogue Scale (P= 0.005) and Verbal Analogue Scale (p=0.003). Patients in the Duloxetine group have more visual and verbal pain score than the placebo group.

In quality of life, there was a significant difference between the two groups before the intervention. Data analysis showed that there was a significant difference between pre and post intervention in Hamilton Anxiety Rating Scale only in duloxetine group.

Also, in terms of quality of life, the subscales of "physical role", "emotional role", "physical pain" and "total score of quality of life" in the duloxetine and placebo groups were significantly different between pre and post intervention.

Discussion: The results from this trial suggests that the use of duloxetine in patients who had spinal surgery can help to better controlling of back pain, in the other hand can cause better psychological condition that affect quality of life.

Keywords: Duloxetine; Spinal fixation; Quality of life; Depression; Anxiety

INTRODUCTION

Low back pain is a common disorder with high disability in physical and mental health, especially if chronic. The life time prevalence of low back pain is about 84% and if prolonged more than 3 months is considered chronic low back pain (CLBP) which prevalence is about 23%.

CLBP can cause high disability, economic burden and low quality of life and the patients with CLBP have significantly greater levels of depression, anxiety and sleep problems [1-4].

Although the definition is clear but the population with CLBP is heterogeneous and is differ in demographics, quality and manifestations of pain and radiological findings.

For treatment of low back pain pharmacological agents like nonsteroidal anti-inflammatory drugs (NSAIDs) are first lines then non pharmacological therapies like spinal manipulation are used. If low back pain is acute in many cases show rapid improvement within 1 month or gradual improvement in 3 months after onset. Treatment with NSAIDs is effective for acute low back pain but in CLBP long term use can cause different side effects like gastro intestinal, cardiac or renal adverse effects.

Duloxetine is an analgestic agent that inhibits serotonin and norepinephrine reuptake (SNRI) with affinity for both transporters. In several studies show that duloxetine can help to decrease pain in chronic pain disorders like CLBP.

Although the exact mechanisms of duloxetine are unknown but

Correspondence to: Arezoo Samadi, Psychiatrist, Fellowship of Psychosomatic Medicine, Iran, Tel: 989123226849; E-mail: arezoosamadi1980@yahoo.com

Received date: July 16, 2020; **Accepted date:** October 05, 2020; **Published date:** October 12, 2020

Citation: Arezoo S, Razieh S, Danial K, Atefeh GJ (2020) Effetiveness of Duloxetine on Pain and Quality of Life in Chronic Back Pain in Patients who had Posterior Spinal Fixation (PSF). J Pain Manage Med 6: 144. doi: 10.35248/2684-1320.20.6.144.

with increasing synaptic levels of serotonin and norepinephrine in spinal and supra spinal pathways produces analgesic effect. With this effect duloxetine has been approved for diabetic neuropathic pain and fibromyalgia. On the other hand duloxetine is an effective drug in treatment of major depressive disorder and generalized anxiety disorder. In some studies have showed that a lots of those with CLBP have depression or anxiety that exacerbate pain, therefore the use of duloxetine with treatment effect on depression and anxiety maybe can help to reduce CLBP.

In this study we want to search the effectiveness of duloxetine on pain and quality of life in patients with CLBP who had a posterior spinal fixation [5-6].

MATERIALS AND METHODS

This randomized, placebo-controlled trial was conducted in neurosurgery department of Rasoul-e Akram hospital in Tehran for 6 months.

In this period of time the patients admitted in clinic and had chronic low back pain (CLBP more than 3 months) and candidate for posterior spinal fixation (PSF) if met inclusion criteria were randomized divided in two groups (duloxetine or placebo) [7-9].

In first step all patients filled the VAS and SF-36 and Hamilton questionnaires. Then all of them had PSF surgery and after the surgery when the patient could take oral drugs the drug group received 30 mg of duloxetine and placebo group received placebo for 6 weeks. After this time all the patients again filled the questionnaires.

Informed consent was obtained from all patients before the trial starting and the protocol was approved by the ethics committee (IR.IUMS.FMD.REC.1398.016) [10].

INCLUSION AND EXCLUSION CRITERIA

Patients older than 18 years old and younger than 80 with CLBP (more than 3 months duration) who were candidate for PSF surgery. All patients had to discontinue any medication that could interfere with their pain such as nonopioid or opioid drugs, antidepressants and anticonvulsants at least for 6 months before surgery.

Non pharmacological pain-relieving procedures such as acupuncture or physical therapies were not allowed during the study [11-13].

Exclusion criteria were as follows: prior use of opioids, depression, use of antidepressants, drug abuse, pregnancy and breast feeding, severe coexisting diseases such as heart failure, severe hypertension, convulsion and kidney dysfunction.

TREATMENT PROTOCOL AND INSTRUMENTS

Patients included in this study divided in two groups (duloxetine and oral duloxetine 30 mg or placebo for 6 weeks. The VAS, Hamilton and SF-36 questionnaires filled two times first before the surgery and second in the end of the trial. If the patients had adverse effects of drug or couldn't tolerate exclude the study placebo) and after PSF surgery were treated with once-daily [14].

VAS QUESTIONNAIRE

The visual analogue scale or visual analog scale (VAS) is a psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two.VAS is the most common pain scale. A review came to the conclusion that VAS and numerical rating scale (NRS) were the best adapted pain scales for pain measurement.For research purposes, and for more detailed pain measurement in clinical practice, the review suggested use of VAS [15-18].

SHORT-FORM-36 HEALTH SURVEY

This patient-reported survey of health is commonly used for quality-of-life assessment.

The following eight domains are routinely determined: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health [19].

Hamilton Anxiety rating scale The Hamilton Anxiety Rating Scale (HAM-A) is a psychological questionnaire used by clinicians to rate the severity of a patient's anxiety. Anxiety can refer to things such as "a mental state...a drive...a response to a particular situation...a personality trait...and a psychiatric disorder. Though it was one of the first anxiety rating scales to be published, the HAM-A remains widely used by clinicians. It was originally published by Max Hamilton in 1959. For clinical purposes, and the purpose of this scale, only severe or improper anxiety is attended to. This scale is considered a "clinical rating" of the extensiveness of anxiety, and is intended for individuals that are "already diagnosed with anxiety neurosis."

The scale consists of 14 items designed to assess the severity of a patient's anxiety. Each of the 14 items contains a number of symptoms, and each group of symptoms is rated on a scale of zero to four, with four being the most severe. All of these scores are used to compute an overarching score that indicates a person's anxiety severity. The Hamilton Anxiety Rating scale has been considered a valuable scale for many years, but the ever-changing definition of anxiety, new technology, and new perceived usefulness. As a result, there have been changes, and challenges, to the original version of the scale over time [20-22].

RESULTS

Each group in Table 1. Groups did not differ for gender distribution, age, education, and marital status. (P>0.05)

According to the Kolmogorov-Smirnov test, distribution of the data was nonparametric, so the Mann-Whitney U test was used to compare the duloxetine and placebo groups and the Wilcoxon signed-rank test was used to Demographic characteristics are represented separately per compare the results before and after the intervention.

As shown in Table 1, the following results were also obtained regarding the difference between the two groups before the intervention: Significant differences were evidenced among groups for Visual Analogue Scale (P= 0.005) and Verbal Analogue Scale (p=0.003). Patients in the Duloxetine group have more visual and verbal pain score than the placebo group.

In terms of quality of life, there was a significant difference between the two groups before the intervention on the "Also, significant differences were evidenced among groups for Hamilton Anxiety Rating Scale (p= 0.17). Patients in the placebo group have more anxiety score than the duloxetine group.

Emotional role" subscale (p=0.035).

After the intervention only Hamilton Anxiety Rating Scale (p=0.001) and "bodily pain" and "general health" subscales of quality of life (p= 0.008, 0.004, respectively) have significant difference between the two groups.

HAM-A, Hamilton Anxiety Rating Scale; SF-36, 36-Item Short Form Health Survey questionnaire. P values less 0.05 were considered statistically significant.

The results after the intervention in the two groups of duloxetine and placebo as well as the comparison of the results of each group before and after the intervention are shown in Table 2.

Using the Wisconsin test, it was shown that there was a significant difference between the visual and verbal VAS scores in both duloxetine and placebo groups between pre and post intervention. Data analysis showed that there was a significant difference between pre and post intervention in Hamilton Anxiety Rating Scale only in duloxetine group.

Also, in terms of quality of life, the subscales of "physical role", "emotional role", "physical pain" and "total score of quality of life" in the duloxetine and placebo groups were significantly different between pre and post intervention. However, the subscales of

Table 1: Demographic characteristics, visual analogue scale, verbal analogue scale, hamilton anxiety Rating scale and Quality of life of the participants before intervention P<0.05.

	No. (%)[a]; Mean (SD)[b] Duloxetine (n=15)	No. (%); Mean (SD) Placebo (n=16)	P value Pre-intervention	P value Post-intervention
Age (Year)[b]	45.13 (15.41)	52 (11.53)	0.31	
Gender[a]			0.213	
Male	7	11		
Female	8	5		
Marital status[a]			0.93	
Single	3	3		
Married	12	13		
Education[a]			0.852	
Elementary	2 (13.3)	4 (25)		
School	4 (26.6)	5 (31.3)		
High school	5 (33.4)	4 (25.3)		
Graduate	4 (26.7)	3 (18.8)		
Visual Analogue Scale[b]	8.80 (1.56)	7.06 (1.48)	0.005*	0.176
Verbal Analogue Scale[b]	3.53 (0.63)	2.68 (0.70)	0.003*	0.41
HAM-A[b]	8.06 (8.21)	16.5 (9.23)	0.017*	0.001*
Sf-36[b]	81.06 (6.74)	84.50 (9.23)	0.276	0.722
Physical Functioning	13.26 (4.55)	16.25 (6.19)	0.134	0.293
Physical Role[b]	4.40 (1.12)	4.87 (1.58)	0.256	0.079
Emotional Role[b]	3.40 (1.05)	4.00 (1.15)	0.035*	0.427
Vitality[b]	14.53 (1.72)	14.06 (2.69)	0.84	0.715
Mental Health[b]	19.60 (1.84)	18.62 (2.55)	0.205	0.229
Social Functioning[b]	5.20 (1.61)	5.68 (0.87)	0.483	0.141
Bodily Pain[b]	8.93 (1.53)	8.00 (1.21)	0.068	0.008*
General Health[b]	11.73 (2.76)	13.00 (2.33)	0.194	0.004*

*HAM-A, Hamilton Anxiety Rating Scale; SF-36, 36-item Short Health Survey questionnaire. P values less 0.05 were considered statistically significant.

Table 2: The result after the intervention in the duloxetine and placebo and the comparison of the result of each group before and after the intervention.

Patient Characteristics	M (SD) Duloxetine (n=15)	M (SD) Placebo (n=16)	P value Duloxetine Group	P value Placebo Group
Visual Analogue Scale	3.53 (1.55)	4.68 (2.30)	0.001*	0.002*
Verbal Analogue Scale	1.86 (0.51)	2.12 (0.88)	0.001*	0.021*
HAM-A	4.46 (4.79)	15.18 (9.86)	0.005*	0.405
SF-36	87.86 (6.31)	87.00 (9.02)	0.006*	0.028*
Physical Functioning	20.66 (4.53)	18.00 (5.95)	0.001*	0.076
Physical Role	6.80 (1.37)	5.68 (1.85)	0.002*	0.041*
Emotional Role	5.13 (1.24)	4.81 (1.27)	0.004*	0.031*
Vitality	14.33 (1.67)	14.43 (2.39)	0.257	0.0392
Mental Health	19.66 (1.04)	18.56 (2.22)	0.863	0.905
Social Functioning	5.46 (0.63)	5.81 (0.54)	0.531	0.627
Bodily Pain	5.20 (1.47)	6.81 (1.64)	0.001*	0.026*
General Health	10.60 (2.13)	12.87 (1.89)	0.027*	0.937

*HAM-A, Hamilton Anxiety Rating Scale; SF-36, 36-Item Short Health Survey questionnaire. P values less 0.05 were considered statistically significant.

"physical function" and "general health" were significantly different only in the duloxetine group between pre and post intervention.

DISCUSSION

Spinal fusion is typically an effective treatment for fractures, deformities or instability in the spine. But study results are more mixed when the cause of the back or neck pain is unclear. In many cases, spinal fusion is no more effective than nonsurgical treatments for nonspecific back pain.

Spinal fusion is surgery to permanently connect two or more vertebrae in spine, eliminating motion between them. Spinal fusion involves techniques designed to mimic the normal healing process of broken bones. During spinal fusion, the surgeon places bone or a bonelike material within the space between two spinal vertebrae. Metal plates, screws and rods may be used to hold the vertebrae together, so they can heal into one solid unit.

Spinal procedures are generally associated with intense pain in the postoperative period, especially for the initial few days. Adequate pain management in this period has been seen to correlate well with improved functional outcome, early ambulation, early discharge, and preventing the development of chronic pain. A diverse array of pharmacological options exists for the effective amelioration of post spinal surgery pain. Each of these drugs possesses inherent advantages and disadvantages which restricts their universal applicability.

The tricyclic antidepressants are a complex group of drugs that have central and peripheral anticholinergic effects and sedative effects. They have central effects on pain transmission, and they block the active reuptake of norepinephrine and serotonin.

A retrospective chart review was conducted in a subset of patients with chronic low back pain and lumbar spinal stenosis managed with low dose tricyclic antidepressants. Of 26 patients, 20 reported improvement in back pain. The majority of patients reported improvement with an initial dose of 10 mg of either amitriptyline or nortriptyline and remained on this dose. Patients with both leg and back pain reported improvement in greater proportion than patients with back pain alone. According to this study tricyclic antidepressants appear to be effective in controlling lumbar spinal stenosis symptoms in this patient population.

Recently, antidepressants such as duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), have accomplished pain relief in persistent and chronic pain as in fibromyalgia, postherpetic neuralgia, diabetic neuropathy,osteoarthritis and musculoskeletal pain]. The analgesic effect of duloxetine is attributed to its ability to enhance both serotonin and norepinephrine neurotransmission in descending inhibitory pain pathways. Moreover, some studies have promoted its use to improve the quality of recovery after surgery and reduce the acute postoperative pain after knee replacement surgery, mastectomy, hysterectomy, and after spine surgery. In addition it can improve postoperative quality of recovery through mood improvement that can be helpful in the postoperative period.

In one randomized clinical trial that done to evaluate the effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy in 230 cases at 8 national cancer institute between 2008-2011showed that at the end of the treatment patients in the duloxetine group reported a larger decrease in average pain (mean change score, 1.06; 95% CI, 0.72-1.40).

In the patients treated with duloxetine 59% reported any decrease in pain vs. 38% in placebo group.

At the end of the treatment when compared with placebo, patients treated with duloxetine reported a greater decrease in the amount that pain had interfered with daily functioning. About pain -related QOL improved to a greater degree for those treated with duloxetine than placebo group.

Another Randomized, Double-blind, Placebo-controlled Crossover Trial that conducted at the outpatient clinic of Anaesthesia and Pain Therapy at the Medical University of Vienna, Austria in 120 cases for evaluating the Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic Component demonstrated that duloxetine was efficacious in the treatment of CLBP with a clear radicular neuropathic component [23,24].

The primary outcome parameter VAS was significantly lower in the duloxetine phase compared with the placebo phase. Although the threshold for an “important improvement” in the individual patient was usually set at a reduction of 20mm on the VAS scale, it was recognized that group differences between placebo and study medication tend to be smaller.

The presence of a neuropathic component in CLBP was associated with higher pain intensity, lower quality of life, and higher healthcare costs compared with CLBP without neuropathic pain component. Therefor duloxetine could help because of neuropathic component of pain.

As randomized, double-blind, placebo-controlled trials on the efficacy of antineuropathic medication in CLBP with a neuropathic component were sparse, interpretation of these results by comparison with other treatment options was challenging [25,26].

A crossover, randomized controlled trial of morphine, nortriptyline, or their combination versus placebo in patients with chronic lumbar root pain did not find a statistically significant difference between placebo and verum agents in the primary outcome parameter, which was average leg pain during the maintenance phase.

Another Randomized Double-blind, Placebo-controlled Trial of Duloxetine Monotherapy in Japanese world Patients With Chronic Low Back Pain that conducted in 58 medical institutions in Japan from May 2013 to July 2014 in 240 patients found that duloxetine was superior to placebo which was consistent with the findings of previous studies conducted. In addition, regarding pain reduction, a reduction of 2 points or at least 30% in the Numeric Rating Scale was generally considered as a clinically significant change.

A greater response among patients with multiple painful sites wad consistent with duloxetine acting on chronic pain mechanisms to modulate descending pain pathways. The presence of multiple painful sites, including the low back, was thought to result from changes in the central nervous system, particularly reduced activity of descending inhibitory pathways, which amplify pain perception. The analysis suggested that the number of painful body sites may be a predictor of response to duloxetine.

In recent study we decided to evaluate the effect of duloxetine in controlling of pain after surgery and its effect on quality of life and anxiety.

According to our study pain in duloxetine-treated group showed greater reduction in compared with placebo-treated group. Also anxiety level in duloxetine group showed significantly decrease. About quality of life scales of physical performance, general

health and overall quality of life score in duloxetine group were significantly improved.

So the effectiveness of surgery on pain is different case by case and sometimes the surgery can't improve the pain completely. In this cases maybe addition of an useful drug can help so much. In this condition the drugs which can relief neurophatic pain like duloxetine are good choices.

The limitations of the current study are clear and include small sample size and short duration of treatment. Due to the relatively short duration of the study treatment, we cannot rule out that the statistically significant effect might be lost at a later time point. In the other hand because of short period of study we couldn't increase the dosage of duloxetine to maximum dose and maybe in upper doses the result of study could change. In this study we couldn't rule out all baseline spine problems so this limitation can effect on the severity of pain and quality of life scores.

Finally the results from this trial and related studies suggest that the use of duloxetine in patients who had spinal surgery can help to better controlling of back pain, in the other hand can cause better psychological condition that affect quality of life. So this group of patients have better life style and less psychological problems like anxiety and depression, but for assessment of long-term efficacy, further trials with larger sample sizes and longer treatment durations are needed.

ACKNOWLEDGMENT

The authors would like to thank all of 50 patients who accepted to participate in this study and neurosurgery ward of Rasoul-e Akram hospital that helped us to accomplish this study.

Although we want to thank from Dr. Abidi Pharmaceuticals that provided our drug and placebo for this study.

REFERENCES

1. Sadosky AB, DiBonaventura M, Cappelleri JC, Ebata N, Fujii K. The association between lower back pain and health status, work productivity, and health care resource use in Japan. J Pain Res. 2015;8:119-130.
2. Deyo RA, Weinstein JN. Low back pain. N Engl J Med. 2001;344:363-370.
3. Fujii T, Matsudaira K. Prevalence of low back pain and factors associated with chronic disabling back pain in Japan. Eur Spine J. 2013;22:432-438.
4. Andersson GB. Epidemiological features of chronic low-back pain. Lancet. 1999;354:581-585.
5. Meucci RD, Fassa AG, Faria NM. Prevalence of chronic low back pain: systematic review. Rev Saude Publica. 2015;49:73-82.
6. Skljarevski V, Zhang S, Desaiah D. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain. 2010;11:1282-1290.
7. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386:743-800.
8. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. Spine J. 2008;8:8-20.
9. Nakamura M, Nishiwaki Y, Ushida T, Toyama Y. Prevalence and characteristics of chronic musculoskeletal pain in Japan. J Orthop Sci. 2011;16:424-432.
10. Suka M, Yoshida K. Low back pain deprives the Japanese adult population of their quality of life: a questionnaire survey at five healthcare facilities in Japan. Environ Health Prev Med. 2008;13:109-115.
11. Hoy D, Bain C, Williams G. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012;64:2028-2037.
12. Webster LR, Markman J. Medical management of chronic low back pain: efficacy and outcomes. Neuromodulation. 2014;17:18-23.
13. Clauw DJ. Diagnosing and treating chronic stematic review. Clin J Pain. 2011;27:169-181.
14. Reme SE, Tangen T, Moe T, Eriksen HR. Prevalence of psychiatric disorders in sick listed chronic low back pain patients. Eur J Pain. 2011;15:1075-1080.
15. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163:2433-2445.
16. Polatin PB, Kinney RK, Gatchel RJ, Lillo E, Mayer TG. Psychiatric illness and chronic low-back pain. The mind and the spine-which goes first? Spine. 1993;18:66-71.
17. Skljarevski V, Ossanna M, Liu-Seifert H. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. Eur J Neurol. 2009;16:1041-1048.
18. Chou R. In the clinic. Low back pain. Ann Intern Med. 2014;160:6-1.
19. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. Best Pract Res Clin Rheumatol. 2010;24:769-781.
20. Clauw DJ. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s). Best Pract Res Clin Rheumatol. 2015;29:6-19.
21. Corrêa JB, Costa LO, de Oliveira NT, Sluka KA, Liebano RE. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. Exp Brain Res. 2015;233:2391-2399.
22. Giesecke T, Gracely RH, Grant MA. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum. 2004;50:613-623.
23. Skljarevski V, Desaiah D, Liu-Seifert H. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine. 2010;35:578-585.
24. Webster LR, Markman J. Medical management of chronic low back pain: efficacy and outcomes. Neuromodulation. 2014;17:18-23.
25. Jones CK, Peters SC, Shannon HE. Efficacy of duloxetine, a potent and balanced serotonergic and noradrenergic reuptake

inhibitor, in inflammatory and acute pain models in rodents. J Pharmacol Exp Ther. 2005;312:726-732.

26. Koch S, Hemrick-Luecke SK, Thompson LK. Comparison of effects of dual transporter inhibitors on monoamine transporters and extracellular levels in rats. Neuropharmacol. 2003;45:935-944.