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Topical treatment of chronic low back pain with a capsicum plaster

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Abstract

The efficacy and tolerance of a capsicum plaster in non-specific low back pain was investigated in a double-blind, randomised, placebo-controlled multicentre parallel group study. A total of 320 patients were randomly assigned to two groups of $n = 160$ subjects treated by the active or the placebo plaster.

The main outcome measures used were a compound pain subscore of the Arhus low back rating scale (continuous variable), and a response criterion of a reduction in pain subscore = 30% from baseline to final assessment (secondary, non-continuous variable). In addition, the partial pain scores, disability and mobility restriction subscores, the total score of the Arhus low back rating scale, the global evaluation of efficacy by investigator and patient, adverse events, a patient questionnaire on use of the plaster, and an evaluation of tolerance by investigator and patient were obtained.

After 3 weeks treatment with capsicum and placebo plaster respectively, the compound pain subscore was reduced by 42% (capsicum) and 31% (placebo) from values on entry. Responder rate was 67% versus 49% ($p = 0.002$). The investigators rated efficacy as "excellent" or "good" by 74% and 36%; the patient's efficacy rating "symptomfree" or "improved" reached 82% and 50%. Adverse local drug reactions were found in 12 patients (7.5%) on capsicum and 5 (3.1%) on placebo. No systemic side-effects were observed. The superiority of the treatment of chronic non-specific low back pain with capsicum plaster compared to placebo was clinically relevant and highly statistically significant. The capsicum plaster offers a genuine alternative in the treatment of non-specific low back pain.
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Keywords: Low back pain; Capsaicin; Capsicum plaster; Clinical study

1. Introduction

Low back pain (LBP) constitutes one of the most difficult and costly medical problems in industrial countries with a prevalence of 25–30% in an adult lifespan and an incidence of about 5% per year (Quittan, 2002). It is the most important cause of occupational disability in individuals under 45 years of age, and the third most important in those over 45 years of age. Gatchel et al. (1995) estimate the total cost (meaning direct and indirect costs) in the US caused by chronic inability to return to work due to LBP at US$ 40–50 billions annually.

Although its consequences are less serious than AIDS, cancer or heart disease, LBP is, according to this estimate, a more costly health problem (Gatchel et al., 1995).

LBP also severely restricts many aspects of life for the individual patient due to: pain, loss of quality of life, total disability for some, and a feeling of helplessness affecting the patient as well as his family. Helplessness is particularly related to the fact that, in more than 90% of cases, no medical reasons can explain the origin of the pain (Grahn et al., 2000; Miedema et al., 1998; Quittan, 2002). In their large scale study on the impact of various chronic diseases on quality of life Sprangers et al. (2000) pointed out, that arthritis and back pain impact most negatively on quality of life of all conditions.

For as long as centrally acting analgesics are not required, drug treatment of chronic pain is usually started with non-steroidal anti-inflammatory drugs (NSAIDs). With as many

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as 8% of the global adult population taking prescribed NSAIDs at any given time this class of drugs belongs to the most widely used ones worldwide (Stiel, 2000). The adverse side effect profile of NSAIDs is well known and a significant cause of morbidity and mortality (Singh et al., 1998; Sung et al., 2000; Hawkey and Langman, 2003; Laine, 2003). Despite high hope for a lesser rate of common adverse side effects such as dyspepsia there is not much difference between COX-2 inhibitors and NSAIDs in that respect (Langman et al., 1999; Nuovo, 2000).

Topically applied capsaicin has gained considerable interest in the local treatment of multiple painful conditions. The molecular basis of its effects has been investigated extensively during the past decade. In the initial phase of treatment, capsaicin causes a local sensation of warmth, which contributes to its therapeutic value. Only in single cases this sensation has been reported to be unpleasant to the patient. Repeated application results in a long lasting desensitization to pain (Caterina and Julius, 2001; Robbins, 2000; Szallasi, 2002). The transient initial local sensation of warmth combined with long lasting desensitization, and the lack of systemic adverse effects make capsicum an alternative worth to be taken into consideration for treatment of local chronic pain. In view of a presumed positive effect in patients with chronic LBP we have investigated the pain relieving potential of a capsicum extract applied as a medicated plaster. This formulation allows a once daily application instead of three to four applications of a cream.

2. Material and methods

2.1. Objective and design of the study

Caucasian patients ($n = 319$) with back pain at rest and during exercise, occurring as part of a chronic non-specific LBP syndrome of at least 3 months' duration, were included in a double-blind, randomised parallel-group study to compare the efficacy and safety of a capsicum plaster with placebo. Before entering the study patients had to meet the inclusion and exclusion criteria. All subjects had to give their written informed consent. The project had been approved by the local ethics committees. The main inclusion criteria were a subjective back pain rating at the time of enrolment of ≥ 5 on an 11-point (0–10) box scale and a history of episodes of back pain for at least 3 months at the time of enrolment.

Patients had to meet general and specific exclusion criteria. General exclusion criteria comprised addiction to alcohol, recreational drugs and medicines, pregnancy and lactation, insufficient contraceptive protection, participation in another clinical trial within the last 4 weeks before entering the study, concomitant psychiatric disorders, such as organic and endogenous psychoses or a pronounced neurotic personality, a surgical procedure required in the immediate future, malignant concomitant diseases, and refusal or withdrawal of informed consent. Specific exclusion criteria included specific causes of back pain (i.e. disc prolapse, spondylolisthesis, ischialgia, spinal stenosis), instability of the spine, spinal fractures, tumors, infections and inflammatory disorders, cervical spine syndrome or osteoporosis, rheumatoid arthritis, Lyme's arthritis, rheumatic factors >40 IU/L, seronegative spondyloarthropathies including ankylosing spondylitis, known chronic skin disease as well as a known hypersensitivity to ingredients of the medicated plaster. Concomitant treatments which could interact with the study medication, had to be discontinued at appropriate intervals before enrolment into the study: *the evening before entry*: paracetamol, physical treatments; *7 days before entry*: NSAIDs, topical medications, muscle relaxants, dose change or start of antihistamines; *4 weeks before entry*: systemic opiates and their derivatives, intra-articular corticosteroids, surgical procedures or nerve blocks in the treatment area, dose change or start of therapy with anti-depressants, anxiolytics or sedatives; *8 weeks before entry*: parenteral corticosteroids, oral corticosteroids equivalent to >10 mg/day prednisolone. All pretreatments and concomitant medications were documented.

The patients were randomly assigned to the two medication groups. The randomisation plan was computer-generated by a member of AFA biometrics department not involved in the study. Randomisation of 360 patients was carried out in blocks of four. Each investigator was supplied with so-called emergency envelopes containing a patient's treatment assignment, which were —if unused—to be returned unopened at the end of the study. If the randomisation code was broken, the investigator who broke the code had to note the date and reason for breaking the code on the appropriate envelope. In that case, the patient involved had to be withdrawn from the study immediately.

The patients—male and female Caucasians between 18 and 75 years of age—were treated for a period of 21 days with control visits after 7 and 21 days.

2.2. Study medication

One 12×18 cm capsicum plaster contains an ethanolic soft extract of cayenne pepper standardized to 22 $\mu g/cm^2$ of capsaicinoids, calculated as capsaicin. This is in accordance with the German monograph 'Capsicum' (Capsicum, 1990), recommending a concentration of 10–40 $\mu g/cm^2$ of capsaicinoids. Based on experimental studies on the release of capsaicin from the plaster and results of a recently published clinical study with a comparable capsicum plaster (Keitel et al., 2001) the plaster treatment time was limited to 4–8 h. This allowed for dosing frequency to be restricted to once daily applications in the morning. Thus, the desired treatment-free breaks in the area of application were provided and patients' individual requirements could be taken into account. The placebo plaster containing no active

substance was identical in shape, size and colour to the test product. The patients had the option of missing out applications on 1–2 days every week. In the cited study (Keitel et al., 2001) almost all patients on capsicum plaster, but also half the patients in the placebo group experienced local sensations of warmth. Pruritus was reported by about half of the patients treated with capsicum and one-third of the placebo group. The occurrence of both sensations on placebo plaster may be explained by the occlusion effect of any plaster formulation.

When planning this study the literature contained no mention of studies with capsicum-containing plasters. The percentage of patients expected to become 'unblinded' was thus based on the only, at that moment unpublished study using a capsicum plaster.

Blinding of such studies is subject to some risk, since it cannot be reliably maintained during treatment. However, the high number of pruritus and burning sensations in the placebo group of the cited study does not allow to definitely conclude which treatment group the individual had been assigned to. For reasons of keeping the number of unblinded patients as low as possible, the patient information explicitly referred to the possibility that a burning sensation or pruritus may be experienced when using the active drug, although absence of this effect permitted no conclusion regarding the group to which the patient had been assigned. An absolutely safe blinding procedure does not exist for capsaicinoids.

The patients were to apply one plaster per day in the morning on the site of maximum pain. They were instructed to keep the plaster in place for 4–8 h.

2.3. Variables

The Arhus Low Back Rating Scale (Manniche et al., 1994), summarises assessments in three disease related dimensions, namely pain, disability and physical impairment (Table 1). For quantification of pain by the patient we used an 11-point box scale (0 = none, 10 = unbearable) with the advantage of being suitable for both visual and audio usage. Pain was assessed in three subcategories: present pain at the time of examination (0–10 points), worst pain within the past 1 or 2 weeks (0–10 points) depending on the interval between visits, and average pain within the past 1 or 2 weeks (0–10 points). The pain dimension in total could give 0–30 points. Disability was measured by a questionnaire regarding 15 daily tasks. A question answered yes = 0 points, answered problematic = 1 point, no = 2 points, giving a total score of 0–30 points. Physical impairment comprised the registration of endurance of the back muscles, measuring back mobility by the modified Schober's test and an assessment of patient's mobility. The endurance of the back muscles was registered by a simple test: The patient was placed prone with legs strapped to a bench and the trunk left unsupported from the level of iliac crest. The length of time that the patient could remain horizontal, and thus clear of the floor, was recorded. Zero seconds scored the maximum of 10 points. One point was deducted from the maximum score for every 30-s interval resulting in a score of 0 points for patients who maintained this position for 270 s and more. In the modified Schober's test, the investigator scored 10 points for 0–19 mm, eight points for 20–29 mm, six points for 30–39 mm, four points for 40–49 mm, two points for 50–59 mm and 0 points for >59 mm. The patient's mobility was assessed in the following way: from a supine position on a flat couch about 80 cm above the floor, the patient stepped onto the floor next to the couch, in the shortest possible time, went to the foot of the couch where he performed a deep knee bend, and returned to the starting position. The score was 0 for less than 10 s, two points for 10–19 s, four points for 20–29 s, six points for 30–39 s, eight points for 40–49 s and 10 points for >49 s. Combined physical impairment yielded from 0 to 30 points. In contrast to the original Arhus index where the use of analgesics/NSAID is recorded and scored, in our study all pain relieving treatments except trial medication were prohibited. All quantified disease dimensions (pain, level of functioning and physical impairment) were weighted so that they were represented in the total score by 30 points each. Combined, they formed a rank scale where a person with a completely healthy back scored 0 points and the hopelessly disabled patient scored 90 points. The compound scale was recorded at all three assessment times (days 0, 7 and 21).

Global assessments of efficacy by patient (free of symptoms–symptoms improved–symptoms unchanged–symptoms worsened) and investigator (excellent efficacy/symptom-free–good efficacy/improvement–adequate efficacy/no change–unsatisfactory efficacy/deterioration) were recorded after 1 and 3 weeks of treatment.

Global assessments of safety by both patient (good–moderate–unsatisfactory) and investigator (good/no ADR–moderate/tolerable ADR–unsatisfactory/severe ADR), adverse events and assessment of compliance comprising

Table 1
Efficacy criteria—Arhus low back rating scale

Score	Scale
A. Arhus back pain score (by patient each)	
1. Current pain	0–10
2. Average pain within the past 2 (1) weeks	0–10
3. Worst pain within the past 2 (1) weeks	0–10
Total maximal pain score = 30	
B. Impairment of movement (by investigator each)	
1. Back mobility	0–10
2. Functional capacity of the back muscles	0–10
3. Patient's mobility	0–10
Total worst movement score = 30	
C. Disability (by patient)	
Questionnaire, 15 items	0–2 each
Total maximum disability score = 30	
Worst global Arhus score = 90 during the last 2 (1) weeks	

the investigator's impression (very good–good–satisfactory–poor) and the count of unused plasters were recorded after 1 and 3 weeks of treatment.

Sociodemographic parameters and vital signs were documented as well.

2.4. Statistical considerations

The statistical analysis was primarily by the intent-to-treat concept. For patients with premature termination of treatment the last assessment under medication was carried forward into the analysis of the final visit, according to the 'last observation carried forward' principle. A per-protocol analysis was performed additionally as a secondary evaluation of the main target variable. The evolution of the combined pain score as derived from the Arhus Rating Scale was defined the primary, continuous variable. Based on this continuous variable a response criterion was established as a secondary, non-continuous variable. Response was defined as a decrease of the combined pain score of at least 30% at the final control visit compared to the baseline value. This difference was considered to be readily perceived by the patient. Furthermore, the percentage of patients showing a $\geq$50% reduction in pain from baseline to final score was calculated to add to the clinical relevance of the results. The group comparison referred to the difference in responder rates between the capsicum and the placebo group. The probability of error was fixed at 5%. The null hypothesis of equal responder rates in both groups had to be refuted in favour of a superiority of one group.

3. Results

3.1. Study population

After completion of the study 319 case record forms could be included into the intent-to-treat analysis, 137 male and 182 female patients, 159 in the capsicum and 160 in the placebo group (Fig. 1). The per-protocol analysis covered 249 cases, 120 on capsicum and 129 on placebo. An early withdrawal from the study was responsible for 23 (14 on capsicum, 9 on placebo) of the 70 exclusions, serious postponement of study visits for 12, insufficient compliance for five, failure to meet the inclusion criteria, non-permitted concomitant diseases or treatment for the other exclusions. Apart from a higher percentage of female patients in the placebo group both groups of patients were comparable with respect to sociodemographic characteristics, history of the back pain, concomitant diseases and treatments, vital signs and pretreatment of the back pain.

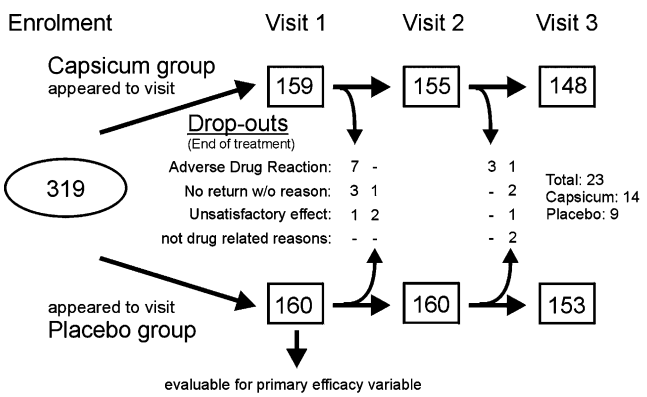

Fig. 1. Group size and number of Drop-outs during the study course.

3.2. Efficacy

With comparable baseline values the compound pain score after 3 weeks of treatment had decreased more markedly in the capsicum group (mean 42%) than in the placebo group (31%) (Fig. 2). The clinically more indicative corresponding median values were 45% on capsicum compared with 27.9% on placebo. The exploratory p-values in the Mann–Whitney U-test showed statistically highly significant differences both with respect to the last recorded value ($p = 0.001$) and the relative reduction in the pain sum score ($p < 0.001$). The results were largely supported by the per-protocol analysis.

The responder rate ($\geq$30% pain reduction) in the capsicum group (67%) exceeded markedly that in the placebo group (49%). The difference was statistically highly significant ($p = 0.002$). Increasing the response criterion to at least 50% reduction in pain score, relative to baseline, the calculated responder rate for capsicum (45%) was nearly twice that for placebo (24%) (Fig. 3).

Table 2 shows the results of the various subscores and the global score of the Arhus low back rating scale.

The subscores summarised in the pain score—current pain, worst pain within the past 2 (1) weeks, average pain within the past 2 (1) weeks—were influenced to a different extent. Mean reduction of current pain from baseline value

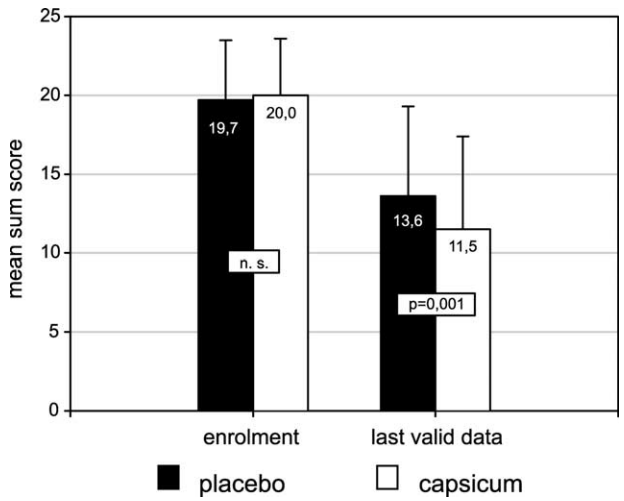

Fig. 2. Mean sum score of three individual pain scales at the start (n.s.) and the end ($p = 0.001$) of treatment periods.

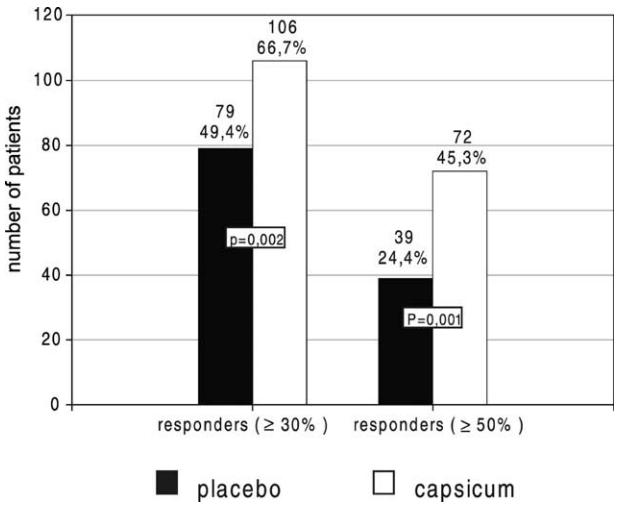

Fig. 3. Responder rates (≥30 or 50% pain reduction) at the end of treatment periods.

to the final assessment was 49 and 37% in the capsicum and the placebo group, respectively. The difference, determined descriptively, was highly significant ($p < 0.001$). The corresponding mean reductions of the worst pain and average pain within the past 2 (1) weeks were 36 versus 25% ($p < 0.002$) and 39 versus 26% ($p < 0.001$).

The compound Arhus subscore of 'impairment of movement' assembling the partial scores 'functional capacity of the back muscles', 'back mobility' and 'patient mobility' decreased from comparable baseline values to those after 3 weeks of treatment by a mean of 21% in the capsicum group and 10% in the placebo group. The improvements of the partial scores reached 12–31% in the capsicum group and 3–15% in the placebo group.

The disability subscore evaluated subjectively by the patient, using a self-assessment questionnaire containing 15 questions on physical and social impairment, showed a mean decrease by 35% in the capsicum group and by 24% in the placebo group.

The mean reduction of the total score of the Arhus Back Index reached 33 and 22% on capsicum and placebo, respectively.

The efficacy ratings of the investigators and patients were largely in agreement. At the final evaluation, the capsicum treatment was rated by the investigators as excellent or good in about three-quarters (74%) of the cases, compared with only 36% for the placebo treatment. A resolution or improvement of symptoms was reported by 82% of active drug patients compared with 50% of the placebo patients.

Table 2
Mean percent reduction of Arhus subscores and total score on treatment with capsicum plaster and placebo plaster, respectively

	Capsicum	Placebo	Significance (p)
Current pain score	49.4	36.9	<0.001
Average pain score	38.9	26.2	<0.001
Worst pain score	36.0	25.0	$=0.002$
Total movement score	20.5	9.5	<0.001
Disability score	34.8	23.9	$=0.001$
Global Arhus score	33.3	22.2	<0.001

3.3. Patient questionnaire, compliance

Sensations of warmth after 1 and 3 weeks of treatment were reported by 90/91% of patients of the capsicum group and 52/49% of the placebo group, respectively. Pruritus was seen considerably less frequently, occurring in 53/61% of capsicum and 38/44% of placebo patients at the first and final follow-up assessments, respectively. The severity of both sensations was assessed by the patients using an 11-point visual analogue scale (0 = not present, 10 = intolerable). The severity of warmth was predominantly ≥5 in the capsicum group versus ≤5 in the placebo group. The severity of pruritus mostly remained ≤3 in both groups. The compliance was rated as very good or good in both groups, with 91 and 93% in the capsicum and the placebo group. Independent of this rating the number of unused plasters was checked. With the exception of 22 out of 319 patients, including six withdrawals, who failed to return their unused plasters, three patients only did not use the minimum planned number of plasters.

3.4. Safety

Adverse events were recorded in 18 patients in the capsicum group and eight patients in the placebo group. Adverse drug reactions with a possible or definitive causal relationship to the trial medication occurred in 12 patients on capsicum and five patients on placebo, and led to premature termination of treatment in nine and one cases, respectively. The predominant symptoms reported for capsicum were an excessively severe sensation of heat or erythema of varying severity. In the placebo group the reactions involved pruritus or vesiculation of varying severity over the plaster application area. On each visit the investigator recorded the skin status of the patient. After 1 week of plaster treatment a predominantly mild to moderate local erythema was documented in 67% of patients on capsicum and 55% of patients on placebo treatment. By the end of the third week of treatment, this proportion had slightly increased to 68% in the capsicum group and decreased to 49% in the placebo group. A predominantly mild local inflammation of the skin developed in 19% of the capsicum and 12% of the placebo patients. The global evaluation of safety by investigators and patients favoured placebo. The investigators rated the safety of the capsicum and the placebo treatment as good in 76 and 84% of the cases. The corresponding ratings of the patients were 66 and 81%.

4. Discussion

Non-specific back pain represents a difficult therapeutic area. All acute forms are known to tend to spontaneous remission. Chronic pain is rather therapy resistant. For the present study, only patients with non-specific back pain of a duration of at least 3 months had been recruited to rule out a tendency to spontaneous remission. In a recent review Guzmán et al. (2001) analysed that multidisciplinary treatments for chronic LBP have been shown to be superior to non-multidisciplinary treatments with respect to pain relief and improvement of function. Essential components of a multimodal treatment strategy in LBP are an extensive information of the patient, a consequent back training, manual therapy, psychological techniques of coping with pain, physiotherapy and the use of analgesic drug treatment. Using only one might allow quantifying its eventual contribution to therapeutic success.

A systematic review of randomised and double-blind controlled trials with NSAIDs for LBP by the Cochrane Collaboration Back Review Group (van Tulder et al., 2000) has indicated statistically significant but small effect in favour of NSAIDs compared with placebo. There was moderate evidence that NSAIDs are not more effective than other drugs for acute LBP, and strong evidence that various types of NSAIDs are equally effective for acute LBP. Sufficient evidence for NSAID efficacy on chronic LBP is still lacking.

In view of the known aetiologic and therapeutic crux of the disease, the results of our investigation of a local treatment using a capsicum plaster are encouraging. Mean decreases of baseline values of the three pain scores (pain at control visit, worst and average pain) from 6.1–7.6 to 3.1–4.8 in the present study—from a category of severe to one of moderate pain—and reductions by >5 points 2–2.5 times as often as under placebo are undoubtedly of clinical relevance. The same applies to the responder rate of 67%. These results confirm those of a study with another capsicum plaster published recently by the same authors (Keitel et al., 2001).

In view of the positive outcome of our study we also calculated number-needed-to-treat (NNTs) for the final values of the ≥ 30 and $\geq 50\%$ improvement criteria. NNTs are treatment-specific and describe the difference between treatment and control in achieving a particular clinical outcome. The obtained NNTs were 5.8 (95% CI: 15.6/3.6) and 4.8 (95% CI: 9.6/3.6) in favour of the capsicum plaster. This is very good in this condition. Except for the known local warmth and—much less—pruritus sensation no adverse drug effects were seen.

The lack of systemic side effects and the easy handling of a plaster formulation compared with semi-solid dosage forms (no contact of active drug with the hand, exact quantity of active substance, uniform release, once daily application) support the favourable risk-benefit ration of the capsicum plaster studied. Capsicum plasters may offer a genuine alternative to NSAIDs in the treatment of chronic non-specific back pain.

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