

# Do analgesics improve functioning in patients with chronic low back pain? An explorative triple-blinded RCT

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## Abstract

**Purpose** Treatment of patients with chronic low back pain (CLBP) aims to reduce disability, improve functional capacity, and participation. Time contingent prescription of analgesics is a treatment modality in CLBP. The impact of analgesics on functional capacity is unknown. Aim of the study was to explore the effect of analgesics on functioning measured by functional capacity evaluation, and self-reported disability in patients with CLBP.

**Methods** Explorative Randomized Placebo-Controlled Clinical Trial was performed in an outpatient pain rehabilitation setting on patients waiting for rehabilitation. Included patients had low back pain lasting >3 months, visual analogue scale worst pain  $\geq 4.0$  cm, and age >18 years. Outcome measures before (T0) and after treatment (T1): functional capacity, pain intensity, Roland Morris Disability Questionnaire. T1: global perceived pain relief. Patient characteristics and psychological questionnaires were assessed. Fifty patients were included in this study and were randomly assigned to 2 weeks treatment or

placebo. Treatment: acetaminophen/tramadol 325 mg/37.5 mg per capsule. Dose: maximum acetaminophen 1,950 mg and tramadol 225 mg per day; treatment and placebo titrated identically. Compliance and side-effects were monitored. Treatment effects between groups over time were compared.

**Results** One patient (treatment group) was lost to follow-up. Forty-nine patients remained in the study. Treatment effects in primary outcomes did not differ significantly between groups. A subgroup of 10 (42 %) patients (treatment group) reported global pain relief (responders) who reduced self-reported disability ( $p < 0.05$ ). Responders had significantly lower catastrophizing scores.

**Conclusion** Overall treatment effects were small and non-significant. A subgroup, however, reported improved functioning as a result of treatment. Responders had lower catastrophizing scores.

**Keywords** Chronic low back pain analgesics · Self-reported disability · Functional capacity evaluation · Psychological factors · Acetaminophen and tramadol

Trial Registration: EudraCT-number 2008-004227-39.

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## Introduction

In the assessment and treatment of patients with chronic low back pain (CLBP), the biopsychosocial model is applied worldwide [1]. According to this model, a patient's pain perception and functioning are influenced by biomedical, psychological and social factors. Damage to tissues, such as muscles, discs, and ligaments, may produce signals that lead to pain perception. A cascade of events in the peripheral and central nerve systems can lead to changes in pain-modulating systems in the nervous system, resulting in sensitization. Although the exact mechanism of sensitization is unknown, this may lead to the chronic pain when tissues have healed or in the absence of tissue damage [2]. Chronic pain may lead to disability defined as "a difficulty in the performance, accomplishment, or completion of an activity" [3]. The relationship between pain intensity and disability is indirect and complex. This complexity is associated with the mediating role of psychological factors such as distress, fear, coping style, and pain cognitions [1, 4]. The strength of the relationship between various psychological factors and disability was found to be weak [5]. According to the Dutch Guidelines for non-specific LBP, analgesics should be prescribed time contingent (<4 weeks), stepwise from light to strong: acetaminophen, NSAID's, combinations of these, tramadol and opioids [6]. The aim is pain reduction and restoration of functioning. Tramadol is an analgesic with weak opioid receptor affinity, and monoaminergic activity, and is suitable for step two at the WHO ladder. It reduces pain and self-reported disability in patients with CLBP [7]. Tramadol and acetaminophen/tramadol reduce pain and self-reported disability in patients with CLBP [7, 8].

Assessment of disability can be done by functional capacity measures. The relationship between pain intensity and functional capacity, measured with functional capacity evaluation (FCE), ranged from non-significant to moderately strong in cross-sectional studies [9]. The impact of reduction of pain intensity on functional capacity is unknown. In one RCT, however, intra-venous opioids led to short-term improvement in lifting capacity [10]. Whether oral analgesics lead to an improvement of functional capacity has not yet been investigated prospectively. The objective of this study was to investigate the effect of the combination of acetaminophen/tramadol on functional capacity and self-reported disability and secondarily, on pain relief in patients with CLBP.

## Methods

### Design

A Randomized Placebo-Controlled Clinical Trial was performed. The main design features were: wash-out,

baseline measurements (T0), randomization, intervention (medication or placebo), and effect measurements (T1). A flowchart describing the study design is presented in Fig. 1. The researcher and the clinician were the same person. Clinician/researcher, tester, patients were blinded to the treatment provided during the study, data-analysis, and writing process of the manuscript until the last version (triple blinded).

### Participants

Participants were recruited from patients with CLBP who were awaiting for an outpatient pain rehabilitation program in two participating rehabilitation centers. Potential participants were informed about the aim of the study (orally and in writing) by the treating physician. Patients were included after they signed informed consent. All included patients received instructions about the study procedures and titration of medication.

The inclusion criteria for the trial were: non-specific CLBP lasting >3 months, a visual analogue scale (VAS) for worst pain in the past week  $\geq 4.0$  cm (to avoid floor effects), age >18 years, on the waiting list for rehabilitation treatment and willing to take the trial medication for 2 weeks (2 weeks were chosen as it suffices for the acetaminophen/tramadol to work with a minimal patient discomfort). Exclusion criteria were: mental (e.g. major psychiatric disorders) or physical causes (e.g. cardiac or pulmonary disorders) leading to reduction in functioning, hypertension, unable/unsafe to participate in FCE, contraindication or known adverse effect for prescribed medication, use of opioids, no willingness to stop pain medication or other treatments for CLBP.

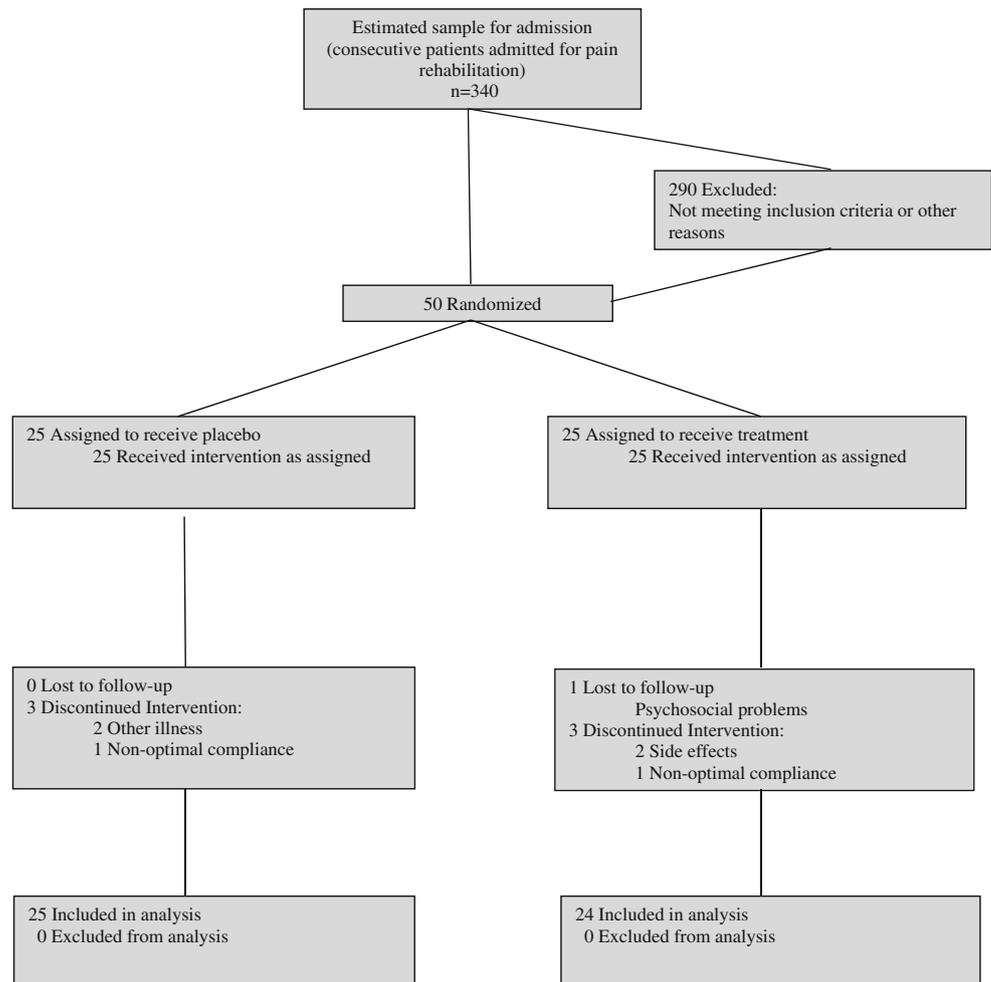
Estimation of the sample size was not possible because a pain-medication study with FCE as the primary outcome measure has not been performed previously. An explorative study with a sample of 25 patients in each group was performed.

### Ethics

The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. The study was approved by the Medical Ethical Committee of the UMCG (EudraCT-number 2008-004227-39). The study took place during the waiting list period for rehabilitation treatment.

### Treatment and placebo

Treatment and placebo were prepared by ACE Pharmaceuticals (Zeewolde, the Netherlands) in compliance with annex 13 EU GMP and checked by a hospital pharmacist.

**Fig. 1** Flowchart

Treatment consisted of acetaminophen/tramadol 325 mg/37.5 mg per capsule or placebo. Treatment and placebo capsules were delivered blinded and randomized per patient in a sealed box with patient numbers 1–50. Medication was titrated to obtain optimal pain reduction with minimal adverse effects [7]. Titration was performed from one capsule two times daily up to a maximum of two capsules, three times daily (placebo or acetaminophen 1,950 mg and tramadol 225 mg). Medication was continued until T1 measurements (2 weeks after T0) were completed. A drop-out rate up to 20 % was expected [8].

#### Randomization

Randomization was done in blocks of 10 for one of the two conditions (placebo or experimental). Immediately after T0, the primary investigator gave the patient a numbered medication box according to randomization scheme. Only the hospital pharmacist had access to the key. The code was broken when writing of the manuscript was in its final stage.

#### Study procedure

After inclusion by the rehabilitation physician, a wash-out period up to 7 days was required for patients who took analgesics prior to the study (dependent on number of tablets and half-time of medication). During this period, the use of all analgesics was eliminated to ensure that effects of study medication were not confounded or interacted by other medication. After wash-out, baseline measurements were completed (T0) and patients received study medication and written instructions. After the titration phase of 1 week, patients used the medication for at least 1 week at a steady dose.

#### Measurements

##### *Outcome measures (T0 and T1):*

Functional capacity was measured using FCE subtests; lifting, carrying, static bending, and dynamic bending. A complete description of the tests can be found elsewhere

[11]. In patients with CLBP construct validity has been established and reliability of the FCE tests is moderate to good [11, 12].

Self-reported disability was measured with the Dutch language version of the Roland Morris Disability Questionnaire (RMDQ, 24 items) which assesses self-reported disability due to low back pain in the past 7 days. Scores range 0–24 (higher scores indicate more disability). Reliability and validity of the RMDQ are good [13, 14].

Patients were asked to rate their global pain change between T0 and T1: worsened pain, same pain, some pain relief or complete pain relief [15]. This measure was administered to identify potential responders on the pain medication. Pain intensity was measured using a 10 cm VAS-score. Patients were asked to rate current pain, and best and worst pain intensity during the previous week [16]. A higher score indicates more intense pain.

#### *Patient characteristics and potential confounding factors*

Patient characteristics were assessed with a self-constructed questionnaire at baseline. Potential confounding factors were psychosocial distress, fear of movement and/or (re)injury, pain cognitions and pain coping. Psychosocial distress was assessed with the Symptom Checklist-90-R (90 items). The total score, Global Severity Index (GSI), ranges from 90 to 450 [17]. Higher scores indicate higher levels of global distress. Reliability and validity of the SCL-90-R are good [17]. Fear of movement and/or (re)injury was measured with the Dutch version of the Tampa Scale of kinesiophobia (TSK; 17 items). It is scored on a 4-point scale. Scores range 17–68. Higher scores indicate higher level of kinesiophobia. Reliability and validity of the TSK, Dutch version, are good [18]. Pain cognitions were measured with the pain cognition list, experimental version (PCL-E), in five subscales: pain impact (scores ranging 17–85), catastrophizing (17–85), outcome efficacy (7–35), acquiescence (4–20), and reliance on health care (5–25) [19]. Each item presents a specific pain cognition statement, and patients indicated agreement or disagreement on a 5-point Likert scale. (1 = totally disagree; 5 = totally agree). Higher scores indicate more impact. Reliability and validity of the PCL-E are sufficient [19]. Coping styles were measured with the Utrecht's coping list (UCL). The following subscales are distinguished: palliative reaction (scores ranging 8–32), active coping (7–28), social support (6–24), avoidance (8–32), expression of emotions (3–12), passive coping (7–28), and coping self-statements (5–20). Higher scores on subscales indicate higher impact on related coping style. Reliability and validity of the UCL are moderate to good [20].

#### *Compliance and side-effects*

Compliance and side-effects were assessed by self-constructed questionnaires. At T0, compliance about stopping the use of analgesics and other treatments for CLBP was assessed. At T1, the applied dosage of the medication and side-effects of medication and FCE were assessed. Remaining capsules were counted to assess trial-medication compliance.

#### *Statistical analysis*

After all data were entered in the database, the hospital pharmacist provided the primary investigator with a code (1, 2) for treatment allocation. The investigators were at that stage unaware of the meaning of 1 or 2. All analyses and interpretations were performed using these codes. Codes were replaced by 'treatment' or 'placebo' at the final stage of writing this manuscript.

Initially, a mixed model analysis was performed with time, group and time–group interaction as predictors for the outcome variables. However, residuals were not normally distributed. Thereafter, distribution of the data was visually assessed in histograms and PP plots. Data were found to be non-normal distributed, therefore non-parametric tests were used. Descriptive statistics were used to describe patient characteristics of both groups. Mann–Whitney *U* test and Chi-square test were used to analyze differences between groups. The Wilcoxon matched-pairs signed rank sum test was used to analyze changes over time. If significant differences were found, changes over time between both groups were analyzed using Mann–Whitney *U* test. Patients who indicated at T1 to have global (some or complete) pain relief were considered responders. Others were considered non-responders. The difference between the number of responders in both groups was analyzed by means of a Chi-square test. Changes in outcomes within responders between T0 and T1 were tested using Wilcoxon matched-pairs signed rank sum test. Comparison of characteristics of responders versus non-responders in the treatment group was performed by means of a two-tailed medians test. All analyses were performed using PASW statistics 18 according to the intention to treat principle. A *p* value <0.05 was considered significant for all analyses.

## **Results**

### *Patient characteristics and potential confounders*

Patients were recruited out of an estimated sample of 340 patients, admitted for outpatient pain rehabilitation between April 2009 and October 2010. None of the patients

**Table 1** Clinical characteristics at baseline (50 patients with chronic low back pain)

Variable	Placebo Median (IQR) N = 25	Treatment Median (IQR) N = 25	p value
Sex (n, (%) male)	9 (36)	7 (28)	0.76
Age (years)	44.0 (32.5–48.0)	42.0 (35.5–50.5)	0.78
Duration of pain (months)	24.0 (12.0–48.0)	18.0 (10.0–48.0)	0.67
VAS-pain current (cm)	4.7 (2.7–7.2)	6.1 (3.2–7.1)	0.26
VAS-pain max (cm)	7.1 (6.1–8.7)	7.4 (6.5–8.5)	1.00
VAS-pain min (cm)	2.0 (0.7–5.1)	4.5 (2.8–5.7)	0.57
Psychological distress (SCL-90-R) (90–450)	123.0 (106.0–146.0)	132.0 (110.0–141.0)	0.57
Kinesiophobia (TSK) (17–68)	33.0 (27.5–39.5)	33.0 (29.5–40.5)	0.78
Pain cognitions (PCL-E)			
Pain impact (17–85)	44.0 (37.0–52.0)	43.0 (37.0–48.0)	1.00
Catastrophizing (17–85)	40.0 (34.0–51.0)	42.0 (35.0–46.5)	0.56
Outcome efficacy (7–35)	20.0 (17.0–22.0)	18.0 (15.5–21.5)	0.59
Acquiescence (4–20)	8.0 (6.0–10.0)	10.0 (7.0–11.0)	0.08
Reliance on health care (5–25)	19.0 (18.0–22.0)	20.0 (19.0–21.0)	0.80
Coping (UCL)			
Palliative reaction (8–32)	17.0 (15.0–20.0)	18.0 (16.5–21.0)	0.57
Active coping (7–28)	18.0 (16.5–20.0)	18.0 (16.0–20.0)	0.78
Social support (6–24)	13.0 (11.5–15.5)	11.0 (10.0–14.0)	0.26
Avoidance (8–32)	16.0 (14.0–18.0)	16.0 (10.0–14.0)	0.78
Expression of emotions (3–12)	5.0 (5.0–6.0)	5.0 (4.0–6.0)	0.77
Passive coping (7–28)	10.0 (8.0–11.5)	11.0 (9.5–12.0)	0.57
Coping self-statements (5–20)	12.0 (10.5–14.5)	13.0 (12.0–14.5)	0.76

VAS visual analogue, SCL-90-R symptom checklist-90-revised, TSK Tampa Scale of Kinesiophobia, PCL-E pain cognition list, experimental version; UCL utrecht's coping list, IQR interquartile range

agreeing to participate ( $n = 50$ ) dropped out before baseline measurements. All were pain-medication free and had no other treatments for CLBP at baseline. Baseline characteristics of patients in both groups are described in Table 1. Differences between both groups were all non-significant.

#### Drop-out, safety and tolerability

One patient in the treatment group was lost to follow-up because of family circumstances. Of the remaining 49 patients, 6 were not compliant to the 2-week medication protocol: 3 in each group. Reasons for not being compliant in the placebo group were unrelated to the study (other illness or sub-optimal compliance). In the treatment group, two patients were not compliant due to side-effects of medication (headache, diarrhea, nausea) and one patient forgot to take medication during 3 days. All other 49 patients remained in the study and were measured at T1. All patients were able to complete FCE tests. No adverse effects from FCE were reported. In the placebo group, 72 % of the patients reported an increase in pain the day after FCE, lasting up to 4 days. In the treatment group, 63 % of the patients reported an increase in pain, lasting up to 5 days. In the placebo group, 19 (76 %) patients used

**Table 2** Daily dose of trial medication after titration

Daily dose	Placebo (N = 25) N (%)	Treatment (N = 24) N (%)
3 × 2 capsules	19 (76)	21 (88)
4 × 1	2 (8)	0
3 × 1	2 (8)	1 (4)
0	2 (8)	2 (8)

N number of patients

maximal dosage of trial medication, in the treatment group, 21 (88 %) (Table 2). Side-effects were reported in 24 % of the patients in the placebo group and in 50 % of the treatment group and consisted of dizziness, nausea, tiredness, diarrhea and short period of skin rash.

#### Outcomes

Differences in primary outcomes between placebo and treatment group were non-significant (Table 3).

Ten (42 %) patients in the treatment group reported some or complete pain relief compared to one patient in the control group ( $p = 0.005$ ) (reported on the global pain change scale). Eight of these responders used maximum dose of medication (two capsules three times a day), and

**Table 3** Differences in outcomes between T0 and T1 for placebo group ( $N = 25$ ) and treatment group ( $N = 24$ )

	Placebo T0 Median (IQR)	T1 Median (IQR)	Treatment T0 Median (IQR)	T1 Median (IQR)
Lifting (kg)	20.0 (12.0–30.0)	17.0 (12.0–34.0)	18.0 (12.0–29.5)	19.0 (12.0–27.0)
Carrying (kg)	24.0 (16.0–37.0)	21.0 (16.0–35.0)	24.0 (16.0–32.5)	20.0 (16.0–43.0)
Static bending (s)	158.0 (90.5–267.0)	192.5 (102.0–237.0)	119.0 (88.0–174.8)	143.0 (90.8–160.5)
Dynamic bending (s/rep)	2.7 (2.5–3.5)	3.0 (2.3–3.7)	2.7 (2.4–3.3)	2.8 (2.4–3.1)
RMDQ (0–24)	13.0 (10.5–15.0)	13.0 (8.0–14.5)	13.0 (10.3–14.8)	11.5 (9.3–15.0)
VAS-pain current (cm)	4.7 (2.7–7.2)	4.5 (2.9–6.9)	6.1 (3.0–7.2)	5.1 (3.3–7.1)
VAS-pain max (cm)	7.1 (6.1–8.7)	7.7 (6.5–8.7)	7.3 (6.4–8.5)	7.4 (5.7–8.1)
VAS-pain min (cm)	2.0 (0.7–5.1)	2.6 (0.8–4.5)	4.4 (2.7–5.5)	3.8 (2.2–5.8)
Global pain change		( $N$ , %)		( $N$ , %)
Pain relief		1 (4)		10 (42)
Same pain or worsened		24 (96)		14 (58)

RMDQ Roland Morris Disability Questionnaire, VAS visual analogue scale, IQR interquartile range

**Table 4** Change in primary outcomes of responders (10 patients with global pain relief in treatment group)

	T0 Median (IQR)	T1 Median (IQR)	$p$ value
Lifting (kg)	21.0 (12.0–30.5)	21.0 (12.0–40.0)	0.10
Carrying (kg)	26.0 (16.5–38.0)	24.0 (18.0–50.0)	0.34
Static bending (s)	134.0 (111.3–180.0)	126.0 (98.5–160.5)	0.51
Dynamic bending (s/rep)	2.7 (2.2–3.2)	2.8 (2.1–3.0)	0.22
RMDQ (0–24)	12.0 (10.8–16.0)	10.5 (7.5–13.8)	0.02*

RMDQ Roland Morris Disability Questionnaire, IQR interquartile range

\* Significant difference ( $p < 0.05$ )

two patients who stopped the medication because of side-effects. Responders showed a tendency to improve on lifting performance ( $p = 0.10$ ). A significant reduction of RMDQ in responders was found (Table 4). Characteristics of responders showed a significantly lower score on subscale catastrophizing of the PCL (median 35.5 versus 44.0 in non-responders,  $p = 0.005$ ), not shown in tables (data available upon request). No other differences between responders and non-responders were found.

## Discussion

The aim of this exploratory study was to investigate the effect of analgesics on functional capacity, next to self-reported disability and pain in patients with CLBP. The differences in primary outcomes were non-significant. Analgesics did not lead to improvement of functional

capacity in patients with CLBP in this study. A subgroup of 10 (42 %) patients in the treatment group (significantly more than in the control group), however, reported global pain relief. They significantly improved on self-reported disability and tended towards improvement in lifting capacity, suggesting that there is a subgroup of responders, who might have a beneficial effect from analgesics. Responders scored significantly lower on the subscale catastrophizing of the PCL which may be a mediator of treatment outcome, as stated in previous research [21].

We choose acetaminophen/tramadol because it is step two of the WHO ladder, to be prescribed for patients who had used acetaminophen or NSAID's with insufficient effect. This analgesic interferes with activation and sensitization of the nociceptive system at several levels [22].

The strength of the study was its rigorous design: RCT, triple blinded and the use of performance-based and self-reported outcome measurements. Use of FCE tests as a primary outcome was used only once previously [10].

Limitation of the study is the small sample size ( $N = 50$ ) and that only one out of seven patients could be included, which limits generalizability. A power analysis could not be made, as no studies had been performed previously in which performance-based measures were used to establish the effect of analgesics on functional capacity. Future studies should use larger samples to analyze effects of acetaminophen/tramadol on FCE outcomes. Post-hoc power analysis, based on the findings of this study, showed that a sample of 182 patients in each group is needed to find a significant difference in results of analgesics on lifting capacity in a FCE in studies with the same design. It may be debated, however, whether the differences are clinically relevant.

In this study, medication was prescribed for a 2-week period. It is unknown how fast sensitization can be reduced. A longer study duration might have given better results. Future studies might consider longer duration of treatment to test whether the 2 weeks used in this study was enough for patients with CLBP.

This study showed that in some patients, the suggested vicious circle of pain, sensitization, and disability might be (partly) broken. The study sample size was too small to explore further possible important characteristics of responders. Pharmacotherapy for pain could be considered as one of the options in an overall management plan [22, 23]. It is important, however, to identify the subgroup of patients who might benefit from pharmacotherapy. Future research should include larger study samples, longer treatment duration, and also patients with a shorter history of complaints. The combination of pharmacotherapy with rehabilitation treatment should also be part of future research.

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**Conflict of interest** There were no conflicts of interest.

## References

- Truchon M (2001) Determinants of chronic disability related to low back pain: towards an integrative biopsychosocial model. *Disabil Rehabil* 23:758–767
- Borenstein DG (2001) Epidemiology, etiology, diagnostic evaluation, and treatment of low back pain. *Curr Opin Rheumatol* 13:128–134
- WHO (2001) International classification of functioning, disability and health (ICF). World Health Organization, Geneva
- Linton SJ (2000) A review of psychological risk factors in back and neck pain. *Spine* 25:1148–1156
- Schiphorst Preuper HR, Reneman MF, Boonstra AM, Dijkstra PU, Versteegen GJ, Geertzen JHB, Brouwer S (2009) Relationship between psychological factors and performance-based and self-reported disability in chronic low back pain. *Eur Spine J* 17:1448–1456
- NHG-Standaard specifieke lagerugpijn (Dutch standard low-back pain) (2005):M54. (Dutch). Huisarts en Wetenschap
- Reig E (2002) Tramadol in musculoskeletal pain—a survey. *Clin Rheumatol* 21:S9–11 discussion S11–2
- Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M (2003) Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther* 25:1123–1141
- Gross DP (2006) Are functional capacity evaluations affected by the patient's pain? *Curr Pain Headache Rep* 10:107–113
- Gross DP, Bhambhani Y, Haykowsky MJ, Rashid S (2008) Acute opioid administration improves work-related exercise performance in patients with chronic back pain. *J Pain* 9:856–862
- Brouwer S, Reneman MF, Dijkstra PU, Groothoff JW, Schellekens JM, Goeken LN (2003) Test-retest reliability of the Isernhagen Work Systems Functional Capacity Evaluation in patients with chronic low back pain. *J Occup Rehabil* 13:207–218
- Gross DP, Battié MC (2003) Construct validity of a kinesio-physical functional capacity evaluation administered within a worker's compensation environment. *J Occup Rehabil* 13:287–295
- Roland M, Morris R (1983) A study of the natural history of low back pain: Part 1: development of a reliable and sensitive measure of disability in low-back pain. *Spine* 8:141–144
- Brouwer S, Kuijjer W, Dijkstra PU, Göeken LN, Groothoff JW, Geertzen JH (2004) Reliability and stability of the Roland Morris Disability Questionnaire: intra class correlation and limits of agreement. *Disabil Rehabil* 26:162–165
- Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL (2000) Defining the clinically important difference in pain outcome measures. *Pain* 88:287–294
- Jensen MP, Karoly P (2001) Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R (eds) *Handbook of pain assessment*, 2nd edn. The Guilford Press, New York, pp 15–34
- Arrindell WA, Ettema JHM (2003) Symptom Checklist. Handleiding bij een multidimensionele psychopathologie-indicator (Manual for a multidimensional psychopathology-indicator). (Dutch). Lisse: Swets Test Publishers
- Vlaeyen JWS, Kole-Snijders AMJ, Boeren RG, van Eek H (1995) Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain* 62:363–372
- Vlaeyen JW, Geurts SM, Kole Snijders AMJ (1990) What do chronic pain patients think of their pain? Towards a pain cognition questionnaire. *Brit J Clin Psychol* 29:383–394
- Schreurs PJG, Willige van de G, Brosschot JF, Tellegen B, Graus GMH (1993) De Utrechtse Coping Lijst: UCL. Omgaan met problemen en gebeurtenissen, herziene handleiding (The Utrecht's Coping List: UCL. Managing problems and events, revised manual). (Dutch). Lisse: Swets Test Publishers
- Spinhoven P, ter Kuile M, Kole-Snijders AMJ, Hutten Mansfeld M, den Ouden DJ, Vlaeyen JWS (2004) Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. *Eur J Pain* 8:211–219
- Lynch ME, Watson CPN (2006) The pharmacotherapy of chronic pain: a review. *Pain Res Manage* 11:11–38
- Nijs J, Meeus M, van Oosterwijk J, Roussel N, de Koning M, Ickmans K, Matic M (2011) Treatment of central sensitization in patients with “unexplained” chronic pain: what options do we have? *Expert Opin Pharmacother* 12:1087–1098