Tapentadol treatment results in long-term pain relief in patients with chronic low back pain and associates with reduced segmental sensitization

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Abstract
Introduction: Chronic low back pain (CLBP) is one of the most common chronic pain conditions in pain practice.
Objectives: In the current study, we describe phenotypes of patients with CLBP based on the status of their endogenous pain modulatory system.
Methods: Conditioned pain modulation (a measure of central pain inhibition), temporal summation (TS, a measure of pain facilitation), and offset analgesia (a measure of temporal filtering of nociception) were evaluated in 53 patients with CLBP at painful and nonpainful sites. Next, in a double-blind, randomized, placebo-controlled trial, 40 patients with defective conditioned pain modulation responses received treatment with tapentadol prolonged-release or placebo for 3 months.
Results: The majority of patients (87%) demonstrated loss of central pain inhibition combined with segmentally increased TS and reduced offset analgesia at the lower back region. During treatment, tapentadol reduced pain intensity more than placebo (tapentadol $-19.5 \pm 2.1$ mm versus placebo $-7.1 \pm 1.8$ mm, $P = 0.025$). Furthermore, tapentadol significantly decreased pain facilitation by reduction of TS responses at the lower back (tapentadol $-0.94 \pm 1.9$ versus placebo $0.01 \pm 1.5$, $P = 0.020$), which correlated with pain reduction ($P < 0.001$).
Conclusion: Patients with CLBP demonstrated different phenotypes of endogenous pain modulation. In patients with reduced conditioned pain modulation, tapentadol produced long-term pain relief that coincided with reduction of signs of pain facilitation. These data indicate that the endogenous pain system may be used as a biomarker in the pharmacological treatment of CLBP, enabling an individualized, mechanism-based treatment approach.

Keywords: Chronic low back pain, Endogenous pain modulation, Conditioned pain modulation, Offset analgesia, Temporal summation

1. Introduction
Chronic low back pain (CLBP) remains one of the most common pain conditions in current pain practice. Treatment is challenging and performed by a multimodal approach, combining pharmacological therapies and nonpharmacological interventions for symptomatic pain relief. Given the often low success rate of treatment in CLBP, an individualized and mechanism-based approach may increase the probability of treatment success. One such approach is to use the endogenous pain modulatory system as biomarker of treatment effect. The endogenous pain system consists of inhibitory and facilitatory descending pain pathways that modulate the activity of nociceptive neurons at the spinal level. Both a loss of pain inhibition and an increase in pain facilitation have been observed in patients with CLBP. However, up to now, we remain uninformed on the association between the endogenous pain system and treatment efficacy in CLBP.

Sensitivity of treatment responses may depend on patient phenotypes based on the status of the endogenous pain system. Frequently used test modalities to evaluate this system are conditioned pain modulation (CPM), temporal summation (TS), and offset analgesia (OA). Conditioned pain modulation is a paradigm where inhibition of a focal noxious stimulus is observed by administration of a second noxious stimulus at a remote area and is an expression of central pain inhibition. Temporal summation is defined by the increase in pain intensity to a repetitive noxious stimulus and is an expression of pain facilitation.
is characterized by profound analgesia after a slight decrease in noxious stimulation and is considered an expression of temporal filtering of nociception.18 By profiling patients at noxious and non-noxious regions, the existence of regional differences in the endogenous pain modulatory system may be observed. Although strong analgesics such as opioids are often used in the management of CLBP, the long-term efficacy has only been sparsely evaluated.7,8,12,24 Different types of opioids have unique effect and side-effect profiles.11 Tapentadol is a bifunctional opioid with activity on the μ-opioid receptor additionally with inhibition of neuronal noradrenaline reuptake.35 The drug is an attractive alternative to conventional opioids as the synergistic interaction at the 2 sites of action produces potent analgesia with less adverse effects.3,5,27 We previously showed that tapentadol induced pain relief because of improvement or restoration of CPM responses in patients with diabetes-induced polyneuropathy and fibromyalgia syndrome.13,29

In the current study, we first determined the endogenous pain modulatory system phenotype of patients with CLBP, and next, given the mechanistic nature of tapentadol-treated patients with reduced or absent CPM responses with tapentadol for 3 months. We hypothesize that pain relief coincides with improvement of the pain modulatory system at a segmental and general level, ie, improvement at noxious and non-noxious sites.

2. Methods

2.1. Patients

Patients diagnosed with nonspecific CLBP were recruited to participate in the trial. Chronic low back pain was defined by the presence of pain in the lumbar region of the spine for at least 3 consecutive months. Patients were considered suitable for inclusion if they had a pain score of at least 5 points on an 11-point numeric rating scale (NRS) for most of the day. Exclusion criteria included specific pathologies causing chronic back pain (such as spinal canal stenosis, disk herniation, spondylolisthesis, etc.), an age <18 or >75 years, a body mass index >40 kg/m², the presence of any medical disease, pregnancy, and a history of psychois, illicit drug, or alcohol abuse. Patients were asked to stop pain medication for at least 4 weeks before the first study visit and refrain from further analgesic medication during the entire study. Written and oral informed consent was obtained from all patients before enrollment into the study. The study protocol was approved by the local institutional review board (Leiden, the Netherlands) and the Central Committee on Research Involving Human Subjects (CCMO, The Hague). The study was registered at the trial register of the Dutch Cochrane Center (Amsterdam, the Netherlands) under identifier 6329 and at the EU clinical trials register with identification number 2015-005259-28. All procedures were performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Study design

Patients were recruited at the pain clinic and invited for a screening visit before enrollment into the study (visit 1). During this screening visit, the inclusion and exclusion criteria were documented and a physical examination was performed. When all inclusion and exclusion criteria were met and the physical examination revealed no abnormalities that precluded enrollment in the study, patients entered into part 1 of the study. Part 1 of the study involved phenotyping, ie, the determination of a footprint of the endogenous pain modulatory system by CPM, OA, and TS testing, and questionnaires to quantify symptom severity.

Only under the condition of a CPM response <12% on both locations, patients entered part 2 of the study. We chose 12% as cutoff value because a CPM response <12% was not observed in healthy young populations; we tested using this specific CPM paradigm (based on 100 subjects, between-day correlation coefficient 0.84 [unpublished observation]). In the current double-blind, randomized, placebo-controlled trial, the effect of treatment (tapentadol) on pain intensity, endogenous pain modulation, and symptom severity was investigated. Patients were randomly assigned to either receive a 12-week tapentadol prolonged release (Grüenthal GmbH, Aachen, Germany) or placebo treatment. The local pharmacy was responsible for randomization and dispensing of the study medication. Tapentadol and placebo tablets were repackaged by the pharmacy to ensure identical appearance without the chance of unblinding the investigator or the patient. Treatment was started at a dose of 50 mg twice daily and weekly increased depending on the amount of pain relief and side-effect profile to a maximum of 250 mg twice daily. In case of unacceptable side effects, dosages were decreased to a dose where side effects were tolerated. During the 12-week treatment period, patients visited the research unit 1, 2, and 3 months (visit 2–4) after the start of treatment and 1 month after treatment ended (visit 5). During these visits, CPM, OA, and TS tests were performed and patients were queried about symptom severity. CPM, OA, and TS were measured on the lower dominant forearm and on the most painful area on the lower back (2 times per location). In addition to these 4-weekly visits, patients were contacted on a weekly basis by telephone to query for pain scores and side effects.

2.3. Conditioned pain modulation and offset analgesia

Conditioned pain modulation was measured using heat pain as test stimulus and cold pain as conditioning stimulus.29 Heat pain was induced using the 3 × 3 thermal probe of the pathway Neurosensory Analyzer (Medoc Ltd., Ramat Yishay, Israel). During heat stimulation, patients quantified the pain intensity level of the stimulus using a computerized potentiometer that ranged from 0 mm (no pain) to 100 mm (worst pain imaginable), allowing for continuous electronic monitoring of the visual analogue scale (eVAS). Cold pain was induced by immersion of the patient’s foot and lower leg in a water bath (Lauda, Lauda-Königshofen, Germany) that could be varied in temperature from 3 to 25°C. At the start of each day, baseline measurements were performed to determine the heat temperature that induced a pain score of 50 to 60 mm (target temperature) and the cold temperature that induced a pain score of 30 to 40 mm. These temperatures were used during the remainder of the study day. For each test, the temperature of the test stimulus increased with 1.5°C/s from baseline (32°C) to the target temperature and kept constant for 10 seconds after which the temperature returned to baseline. The eVAS score of the test stimulus (heat pain) with and without the conditioning stimulus (cold pain) was determined to quantify CPM. The conditioning stimulus was applied 25 seconds before the start of the test stimulus and ended simultaneously with the test stimulus. Patients were specifically instructed to only rate pain intensity of the test stimulus.

Offset analgesia was measured using a heat pain paradigm as described previously.28 In short, the temperature of the probe was increased from the baseline temperature to the target temperature (50–60 mm). After 5 seconds, the temperature of the heat probe was raised by 1°C for 5 seconds and next returned to the target temperature (decrease of 1°C) for another 20 seconds. During heat stimulation, patients continuously rated the intensity...
of the train of repetitive stimuli. A paired-sample t test was used to compare CPM, OA, and TS between the different test locations.

The overall treatment effects (corrected for baseline) on CPM, OA, TS, spontaneous pain scores, and questionnaires (visit 1–4) were analyzed using a linear mixed model with treatment as fixed effect and patient as random effect to account for repeated measurements over time. An analgesia responder rate analysis was performed to evaluate the proportion of patients who achieved predefined response rates in the range between 0% and 100%. The response rate was calculated by the proportion of pain relief during the treatment period (visit 2–4) compared with baseline. A Kolmogorov–Smirnov test was used to compare treatment distributions. Correlations between CPM, OA, TS, spontaneous pain, and questionnaires were analyzed using the Pearson correlation. All statistical analyses were performed in SPSS Statistics for Windows v25 (IBM Corp., Armonk, NY). P-values < 0.05 were considered significant. Data are presented as mean ± SD unless otherwise stated.

3. Results

3.1. Study part 1—phenotyping

A total of 68 patients were assessed for eligibility to participate in the study of whom 15 patients were excluded based on the inclusion and exclusion criteria (Fig. 1). The results of the 3 test modalities of the endogenous pain modulatory system (CPM, OA, and TS), obtained in the total population of 53 patients, are given in Figures 2A–C. On average, a pain facilitatory CPM response was observed on the arm (–7.8 ± 2.7%) and an absent response on the lower back (0.5 ± 2.4%); P = 0.08 (Fig. 2A). Offset analgesia was significantly reduced on the lower back compared with the arm (Fig. 2B): 89.1 ± 3.4% (arm) and 70.6 ± 5.2% (lower back); P = 0.004. Temporal summation was significantly increased on the lower back compared with the arm: 0.4 ± 0.2 (arm) and 1.1 ± 0.3 (lower back; P = 0.02).

Patients were stratified according to their CPM response into a group with a CPM response <12% and a group with a response ≥12%.

3.1.1. Conditioned pain modulation% ≥12%

Conditioned pain modulation responses were ≥12% (both measurement sites) in 7 (13%) of 53 patients with an average CPM% of 28.5 ± 10.8% on the arm and 15.8 ± 15.3% on the lower back. The overall treatment effects (corrected for baseline) in the group with a CPM response ≥12% and the group with a CPM response <12% were analyzed using a linear mixed model with treatment as fixed effect and patient as random effect to account for repeated measurements over time. An analgesia responder rate analysis was performed to evaluate the proportion of patients who achieved predefined response rates in the range between 0% and 100%. The response rate was calculated by the proportion of pain relief during the treatment period (visit 2–4) compared with baseline. A Kolmogorov–Smirnov test was used to compare treatment distributions. Correlations between CPM, OA, TS, spontaneous pain, and questionnaires were analyzed using the Pearson correlation. All statistical analyses were performed in SPSS Statistics for Windows v25 (IBM Corp., Armonk, NY). P-values < 0.05 were considered significant. Data are presented as mean ± SD unless otherwise stated.

3.2. Study part 2—conditioning analgesia

A total of 68 patients were assessed for eligibility to participate in the study of whom 15 patients were excluded based on the inclusion and exclusion criteria (Fig. 1). The results of the 3 test modalities of the endogenous pain modulatory system (CPM, OA, and TS), obtained in the total population of 53 patients, are given in Figures 2A–C. On average, a pain facilitatory CPM response was observed on the arm (–7.8 ± 2.7%) and an absent response on the lower back (0.5 ± 2.4%); P = 0.08 (Fig. 2A). Offset analgesia was significantly reduced on the lower back compared with the arm (Fig. 2B): 89.1 ± 3.4% (arm) and 70.6 ± 5.2% (lower back); P = 0.004. Temporal summation was significantly increased on the lower back compared with the arm: 0.4 ± 0.2 (arm) and 1.1 ± 0.3 (lower back; P = 0.02).

Patients were stratified according to their CPM response into a group with a CPM response <12% and a group with a response ≥12%.

3.2.1. Conditioned pain modulation% ≥12%

Conditioned pain modulation responses were ≥12% (both measurement sites) in 7 (13%) of 53 patients with an average CPM% of 28.5 ± 10.8% on the arm and 15.8 ± 15.3% on the lower back. The overall treatment effects (corrected for baseline) in the group with a CPM response ≥12% and the group with a CPM response <12% were analyzed using a linear mixed model with treatment as fixed effect and patient as random effect to account for repeated measurements over time. An analgesia responder rate analysis was performed to evaluate the proportion of patients who achieved predefined response rates in the range between 0% and 100%. The response rate was calculated by the proportion of pain relief during the treatment period (visit 2–4) compared with baseline. A Kolmogorov–Smirnov test was used to compare treatment distributions. Correlations between CPM, OA, TS, spontaneous pain, and questionnaires were analyzed using the Pearson correlation. All statistical analyses were performed in SPSS Statistics for Windows v25 (IBM Corp., Armonk, NY). P-values < 0.05 were considered significant. Data are presented as mean ± SD unless otherwise stated.

3.2.2. Conditioned pain modulation% <12%

Conditioned pain modulation responses were <12% (both measurement sites) in 46 (87%) of 53 patients with an average CPM% of 11.5 ± 9.7% on the arm and 5.6 ± 7.5% on the lower back. The overall treatment effects (corrected for baseline) in the group with a CPM response ≥12% and the group with a CPM response <12% were analyzed using a linear mixed model with treatment as fixed effect and patient as random effect to account for repeated measurements over time. An analgesia responder rate analysis was performed to evaluate the proportion of patients who achieved predefined response rates in the range between 0% and 100%. The response rate was calculated by the proportion of pain relief during the treatment period (visit 2–4) compared with baseline. A Kolmogorov–Smirnov test was used to compare treatment distributions. Correlations between CPM, OA, TS, spontaneous pain, and questionnaires were analyzed using the Pearson correlation. All statistical analyses were performed in SPSS Statistics for Windows v25 (IBM Corp., Armonk, NY). P-values < 0.05 were considered significant. Data are presented as mean ± SD unless otherwise stated.

3.2.3. Temporal summation

Temporal summation was calculated by the difference in the NRS (mean peak value) between the single pin prick stimulus and the 10th pin prick stimulus without CS. To correct for variation in the peak responses between patients and calculated as: Temporal summation = (eVAS/peak eVAS) × 100. Temporal summation was calculated by the difference in the NRS between the single pin prick stimulus and the 10th pin prick stimulus without CS.
lower back (P = 0.10; Fig. 2D). Offset analgesia responses (eVASc) in this population were 90.5 ± 6.9% on the arm and 68 ± 20.3% on the lower back (P = 0.23; Fig. 2E). Temporal summation was 0.9 ± 0.4 and 0.7 ± 0.7 on the arm and lower back, respectively (P = 0.85; Fig. 2F).

3.1.2. Conditioned pain modulation <12%
Conditioned pain modulation responses <12% (both measurement sites) were observed in 46 (87%) patients with an average CPM% of −12.8 ± 18.2% on the arm and −2.3 ± 19.6% on the lower back (P = 0.01; Fig. 2G). Offset analgesia responses in this population were 88.9 ± 3.7% (arm) and 71.0 ± 5.4% (lower back; P = 0.009; Fig. 2F), and TS was 0.4 ± 0.3 (arm) and 1.2 ± 0.3 (lower back; P = 0.01; Fig. 2G). No correlation was observed between the magnitudes of CPM, OA, and TS.

3.1.3. Pain and questionnaires
Average reported pain scores in the total population were 64.0 ± 11.2 mm. Most patients reported nociceptive pain. The PainDetect questionnaire indicated that a neuropathic pain component was possibly present in 17% of patients and likely present in 9% with mild neuropathic pain symptoms according to the NPSI and moderate influence on physical disability according to the RMDQ (Table 1). No differences were observed between patients with or without CPM in pain scores or any of the items scored in the questionnaires. Furthermore, no correlation was observed between CPM, OA, and TS with the spontaneous pain scores and questionnaires.

3.2. Study part 2—tapentadol treatment
A total of 46 patients with CPM <12% were eligible for treatment randomization of whom 6 patients dropped out (Fig. 1). No significant differences in baseline characteristics were observed between the 2 treatment groups (Table 2). The average daily drug dose after the titration period was 302.5 ± 93.9 mg for the tapentadol group and 357.5 ± 90.7 mg for the placebo group (P = 0.07). Side effects were reported in 18 patients randomized to tapentadol and in 8 patients randomized to placebo, with more side effects reported by patients treated with tapentadol (n = 45) than placebo (n = 17; P < 0.001; Table 3).

3.2.1. Pain and questionnaires
No baseline differences were observed in spontaneous pain questionnaire scores (Table 2). Tapentadol reduced spontaneous pain scores compared with placebo with an average
reduction during treatment of $-19.5 \pm 2.1$ mm (tapentadol) and $-7.1 \pm 1.8$ mm (placebo; $P = 0.03$; 95% confidence interval [CI] $-16.6$ to $-1.2$ mm; Fig. 3A). Furthermore, analysis of analgesia responder rates (0%–100%) showed a treatment effect in favor of tapentadol ($P < 0.001$, Fig. 3B). No effect of treatment was observed on any item of the questionnaires.

| Table 1 | Patient characteristics. |
|---------|--------------------------|
|         | Total population | CPM <12% | CPM ≥12% |
| Men/women (n) | 33/20 | 28/18 | 5/2 |
| Age (y)—mean (SD) | 62.2 (10.9) | 62.0 (11.3) | 63.6 (8.8) |
| Weight (kg)—mean (SD) | 82.8 (17.0) | 84.4 (17.2) | 71.1 (12.2) |
| Height (cm)—mean (SD) | 174.4 (8.9) | 174.8 (9.0) | 172.1 (9.0) |
| Disease duration (y)—mean (SD) | 20.5 (17.4) | 19.9 (16.7) | 24.4 (22.6) |

| PainDetect |         |         |         |
|-------------|---------|---------|---------|
| Pain score (mm)—mean (SD) | 64.0 (11.2) | 64.3 (11.1) | 61.4 (12.2) |
| Neuropathic symptom score—mean (SD) | 10.3 (5.7) | 11.1 (5.7) | 5.6 (3.6) |
| Score 13–18 (n, %) | 9 (17.0) | 9 (19.6) | 0 (0) |
| Score 19–38 (n, %) | 5 (9.4) | 5 (10.9) | 0 (0) |

| NPSI overall—mean (SD) | 0.2 (0.2) | 0.3 (0.2) | 0.2 (0.2) |
| Burning pain | 0.2 (0.3) | 0.2 (0.3) | 0.1 (0.1) |
| Deep pressing pain | 0.3 (0.2) | 0.3 (0.2) | 0.2 (0.1) |
| Paroxysmal pain | 0.3 (0.3) | 0.3 (0.3) | 0.2 (0.2) |
| Evoked pain | 0.2 (0.2) | 0.2 (0.2) | 0.1 (0.2) |
| Paresthesia/dysesthesia | 0.2 (0.2) | 0.2 (0.2) | 0.1 (0.2) |

| RMDQ—mean (SD) | 11.4 (4.7) | 11.0 (4.4) | 13.7 (6.6) |

| Table 2 | Baseline characteristics per treatment group. |
|---------|---------------------------------------------|
|         | Tapentadol (n = 20) | Placebo (n = 20) |
| Men/women (n) | 16/4 | 11/9 |
| Age (y)—mean (SD) | 64.9 (12.5) | 60.8 (9.7) |
| Weight (kg)—mean (SD) | 88.3 (19.8) | 84.3 (14.0) |
| Height (cm)—mean (SD) | 175.3 (8.0) | 175.5 (10.8) |
| Disease duration (y)—mean (SD) | 22.4 (20.3) | 15.3 (13.8) |

| PainDetect |         |         |         |
|-------------|---------|---------|---------|
| Pain score (mm)—mean (SD) | 67.0 (12.2) | 62.5 (10.7) |
| Neuropathic symptom score—mean (SD) | 10.3 (5.9) | 12.0 (5.7) |
| Score 13–18 (n, %) | 3 (15.0) | 4 (20) |
| Score 19–38 (n, %) | 2 (10.0) | 3 (15) |

| NPSI overall—mean (SD) | 0.3 (0.2) | 0.2 (0.2) |
| Buring pain | 0.3 (0.3) | 0.2 (0.2) |
| Deep pressing pain | 0.3 (0.2) | 0.2 (0.2) |
| Paroxysmal pain | 0.4 (0.3) | 0.3 (0.2) |
| Evoked pain | 0.2 (0.2) | 0.2 (0.2) |
| Paresthesia/dysesthesia | 0.3 (0.3) | 0.2 (0.2) |

| RMDQ—mean (SD) | 11.9 (4.0) | 10.9 (5.1) |

| CPM, conditioned pain modulation; NPSI, Neuropathic Pain Symptom Inventory; RMDQ, Roland–Morris Disability Questionnaire. |

CPM, conditioned pain modulation; eVASc, electronic visual analogue scale corrected; NPSI, Neuropathic Pain Symptom Inventory; OA, offset analgesia; RMDQ, Roland–Morris Disability Questionnaire; TS, temporal summation; VAS, visual analogue scale.
Table 3
Number of patients reporting side effects.

| Side effects (n, %)       | Tapentadol (n = 20) | Placebo (n = 20) | P     |
|--------------------------|---------------------|------------------|-------|
| Dizziness                | 9 (45)              | 3 (15)           |       |
| Nausea                   | 9 (45)              | 4 (20)           |       |
| Vomiting                 | 1 (5)               | 0 (0)            |       |
| Tiredness                | 6 (30)              | 5 (25)           |       |
| Headache                 | 5 (25)              | 1 (5)            |       |
| Shaking                  | 1 (5)               | 1 (5)            |       |
| Itchiness                | 4 (20)              | 1 (5)            |       |
| Vivid dream              | 3 (15)              | 1 (5)            |       |
| Obstipation              | 4 (20)              | 0 (0)            |       |
| Dry mouth                | 2 (10)              | 0 (0)            |       |
| Dyspnea                  | 0 (0)               | 1 (5)            |       |
| Urinary hesitancy        | 1 (5)               | 0 (0)            |       |
| Total (n)                | 45                  | 17               | <0.001|

3.2.2. Conditioned pain modulation, offset analgesia, and temporal summation

At baseline, CPM, OA, and TS values were similar between the 2 study arms (Table 2). No effect of tapentadol was observed on CPM or OA on any location (CPM arm: 16.9 ± 4.3 versus 10.1 ± 4.3, P = 0.285, 95% CI −4.4 to 14.5; CPM lower back: 8.5 ± 5.7 versus 5.0 ± 5.7, P = 0.669, 95% CI −9.6 to 14.9; OA arm: 10.5 ± 6.8 versus −7.5 ± 6.7, P = 0.271, 95% CI −6.5 to 22.5; and OA lower back: 12.3 ± 7.3 versus −5.0 ± 7.2, P = 0.097, 95% CI −2.5 to 28.4 [all data are represented as tapentadol versus placebo]). Tapentadol did show a significant effect on TS but only on the lower back: −1.2 ± 0.4 (tapentadol) versus 0.02 ± 0.4 (placebo; P = 0.02; 95% CI −1.7 to −0.2 (Fig. 4). A significant correlation was present between these TS responses and the corresponding pain scores (r² = 0.99; P < 0.0001; Fig. 5). No effect of tapentadol on TS was observed on the arm compared with placebo: −0.3 ± 0.4 versus 0.1 ± 0.4 (P = 0.534, 95% CI −1.2 to 0.6), and responses did not correlate to corresponding pain scores (r² = 0.06, P = 0.698). Also, no correlations were observed between pain scores and CPM or OA responses.

Figure 3. (A) Change in the pain score compared with baseline during and after treatment with tapentadol (light blue circles) and placebo (dark blue squares). The gray bar indicates the treatment period. Tapentadol significantly reduced spontaneous pain scores compared with placebo (P = 0.025). (B) Graph of the analgesia responder rate for predefined response rates in the range between 0% and 100%. ΔVAS, delta visual analogue scale; *Significant change in the pain score between tapentadol and placebo.

4. Discussion

In the first part of this study, we characterized the pain modulatory system in patients with CLBP at the location of their most intense pain and a reference site (arm) using CPM, OA, and TS. Segmental differences were observed for all 3 test modalities. In the second part of the study, patients with defective CPM treated with tapentadol for 3 months had significant consistent pain relief during the treatment period with a correlated reduction in TS responses at the painful lower back. No effect on CPM was observed.

4.1. Phenotype of the pain modulatory system

Three test modalities were used to evaluate the efficacy of the pain modulatory system: CPM, TS, and OA. Conditioned pain modulation, which is considered a surrogate marker for central pain inhibition, has been extensively studied in many chronic pain syndromes including CLBP. A recent meta-analysis evaluating CPM in patients with CLBP demonstrated reduced CPM responses in patients compared with controls. This agrees with the results of this study where the majority of patients with CLBP (87%) showed aberrant CPM responses. A segmental effect of CPM was observed in this population of CLBP with absent CPM responses on the lower back and a pain facilitatory response on the arm (negative CPM). These findings suggest multisegmental pain facilitation possibly in combination with segmental inhibition at the site of the lower back. This is in agreement with earlier studies in patients with CLBP, which show, eg, widespread hyperalgesia in subpopulations.

In patients with reduced CPM responses, TS responses were significantly increased on the lower back relative to the arm, which we suggest to be related to segmental pain facilitation. Although several studies found indications of central sensitization in patients with CLBP, only a few show differences in magnitude of TS at the site of pain compared with a reference site. In line with our findings, Gerhardt et al. showed segmental pain facilitation with greater TS responses on the lower back compared with the hand. Interestingly, this was observed only in a subgroup of patients with chronic widespread pain. This possibly reflects that CPM and TS responses are differentially impaired in subsets of patients with CLBP.

Offset analgesia responses were reduced on the lower back compared with the arm in our population of patients with CLBP. OA is considered a temporal and spatial filtering mechanism of pain able to...
induce poststimulus pain inhibition. The underlying neurophysiological mechanism has not been fully understood where both central and peripheral processes have been proposed. Reduced OA responses have been observed in patients with diabetic polyneuropathy, fibromyalgia, and CRPS. The current study is the first to study OA responses in a large population of patients with CLBP.

![Figure 4](image4.png)

**Figure 4.** CPM, OA, and TS responses during and after treatment with tapentadol (light blue circles) and placebo (dark blue squares) for the arm (A, C, and E) and the lower back (B, D, and F). The gray bar indicates the treatment period. Tapentadol significantly decreased temporal summation responses on the lower back compared with placebo (significant change indicated by asterisk; overall effect: $P = 0.020$). CPM, conditioned pain modulation; eVASc, electronic visual analogue scale corrected for the peak response; NRS, numerical rating scale; OA, offset analgesia; TS, temporal summation.

![Figure 5](image5.png)

**Figure 5.** Correlation between TS responses of the lower back and spontaneous pain scores for tapentadol (A) and placebo treatment (B). A significant correlation was observed for the patients treated with tapentadol ($r^2 = 0.99, P < 0.001$). No correlation was observed after treatment with placebo ($r^2 = 0.06, P = 0.695$). The numbers in the graph indicate the treatment month. ΔVAS, delta visual analogue scale; ΔTS, delta temporal summation.
and also the first to evaluate OA on 2 separate body locations. We previously showed that a ΔVAS of 88% separates normal from abnormal OA responses in neuropathic pain patients (with responses <88% defined as abnormal). Extrapolation of this cutoff to this study suggests that OA was abnormal on the lower back (but not arm) in the majority of our patients irrespective of CPM condition. This suggests that OA is segmentally affected comparable with our observations in TS. Of note, as this is the first study which performed OA responses on the lower back, we are not informed on OA responses at this location in a healthy population.

In agreement with literature, our data indicate that multiple phenotypes exist within the CLBP population. Most patients in our sample displayed reduced pain inhibitory responses combined with segmental sensitization and segmentally reduced OA responses. This phenotype may require a specific treatment approach aimed at restoration of these specific responses to cause effective and long-term pain relief.

4.2. Tapentadol treatment

We were unable to detect a significant effect of tapentadol treatment on CPM. We relate this to an appreciable increase of CPM during placebo treatment. The magnitude of the CPM increase (about 20%) was in accordance with previously observed increases in patients with diabetic polyneuropathy and fibromyalgia syndrome. In agreement with literature, we did observe a significant analgesic effect with almost 50% of patients that experienced 50% of pain relief during treatment. In contrast to our previous studies, we did not observe a correlation between analgesia and CPM% responses. This might indicate that in patients with CLBP, pain relief is to a lesser extent or less consistently associated with CPM improvement and suggests a rather distinct mechanistic effect of tapentadol in different pain syndromes.

Tapentadol significantly reduced TS on the lower back. To the best of our knowledge, no other studies investigated the influence of tapentadol on pain facilitation. However, previous studies did find evidence for an effect of opioids on TS. For example, codeine, morphine, oxycodone, and remifentanil reduce TS responses. Whether the observed reduction of TS in the current study is mainly related to the effect of tapentadol on the μ-opioid receptor or to the noradrenergic component of the drug is unknown. In contrast to CPM, the effect of tapentadol on TS responses at the lower back region was significantly correlated to spontaneous pain scores. This suggests that pain relief by tapentadol in our CLBP population may be mediated by a reduction in pain facilitation rather than by an improvement of top-down pain inhibition. Tapentadol had no effect on TS responses on the reference site, but this was expected because these responses were normal before treatment. Giving the specific phenotype of patients in our study, it remains unknown what the effect of tapentadol would be in patients with normal TS responses at the painful back.

Finally, despite the observation of profound and long-term analgesia, no effect of tapentadol was observed on OA irrespective of location. This agrees with previous studies showing that centrally acting drugs, including tapentadol, do not influence OA responses. This suggests that OA is a biomarker of defective pain modulation which is not affected by either the opioidergic or the noradrenergic components of tapentadol treatment. It additionally suggests that OA is a secondary phenomenon that is not part of any of the mechanistic pathways through which pain in patients with CLBP is experienced or may be influenced.

Some limitations have to be addressed for this study. First, the study has a small sample size and should be considered as hypothesis generating. Further research needs to be performed to confirm our findings. Second, outcome measurements such as pain, CPM, and TS may spontaneously change over time (without intervention). We performed our study as standardized as possible but cannot rule out any influence of spontaneous changes over time. Third, we used a CPM cutoff value of 12% as biomarker of impaired CPM. Further studies should address the influence of CPM cutoff values on tapentadol treatment effect.

Disclosures

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