# CLINICAL—PANCREAS

## Pregabalin Reduces Pain in Patients With Chronic Pancreatitis in a Randomized, Controlled Trial

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**BACKGROUND & AIMS:** Pain is a disabling symptom for patients with chronic pancreatitis (CP) and difficult to treat. Evidence from basic science and human studies indicates that pain processing by the central nervous system is abnormal and resembles that observed in patients with neuropathic pain disorders. We investigated whether agents used to treat patients with neuropathic pain are effective in CP. **METHODS:** We conducted a randomized, double-blind, placebo-controlled trial to evaluate the effects of the gabapentoid pregabalin as an adjuvant analgesic. We measured pain relief, health status, quality of life, and tolerability in 64 patients with pain from CP; they were randomly assigned to groups given increasing doses of pregabalin or placebo (control) for 3 consecutive weeks. The primary end point was pain relief, based on a visual analogue scale documented by a pain diary. Secondary end points included Patients' Global Impression of Change (PGIC) score, changes in physical and functional scales, pain character, quality of life, and tolerability. **RESULTS:** Pregabalin, compared with placebo, caused more effective pain relief after 3 weeks of treatment (36% vs 24%; mean difference, 12%; 95% confidence interval, 22%–2%; $P = .02$). The percentage of patients with much or very much improved health status (PGIC score) at the end of the study was higher in the pregabalin than the control group (44% vs 21%; $P = .048$). Changes in physical and functional scales, pain character, quality of life, and number of serious adverse events were comparable between groups. **CONCLUSIONS: In a placebo-controlled trial, pregabalin is an effective adjuvant therapy for pain in patients with CP.**

*Keywords:* Abdominal Pain; Central Pain Processing; Pancreas; Clinical Trial.

Upper abdominal pain is a dominant feature of chronic pancreatitis (CP), and its treatment remains a major clinical challenge.[1] Analgesic medication is part of the initial treatment and often includes opioids in the absence of pathology suitable for endoscopic or surgical interventions.[2] However, opioid-based analgesia often only shows limited effectiveness in these patients and is frequently accompanied by undesirable side effects.[3] Basic studies of pancreatic nerves and experimental human pain research have provided evidence that pain processing is abnormal in patients with CP and in many patients resembles that seen in neuropathic pain disorders.[4–7] Gabapentoids, including pregabalin, have effectively been used to treat various neuropathic pain disorders, including diabetic neuropathy, postherpetic neuralgia, and neuropathic pain of central origin.[8–13] Based on the limited effectiveness of conventional opioid-based analgesic approaches to CP pain, and the finding that pancreatitis pain is accompanied by similar alterations of central pain processing as seen in neuropathic pain, we hypothesized that pregabalin could be effective as an adjuvant treatment to decrease pain associated with CP. The aims of this study were to evaluate the effects of pregabalin on pain relief, health status, and quality of life and to understand the tolerability in patients with CP.

### Patients and Methods

#### *Study Oversight*

The study was an investigator-initiated, double-blind, placebo-controlled, parallel-group study of increasing doses of pregabalin conducted in The Netherlands and Denmark. Pfizer donated pregabalin and identical capsules containing placebo but was not involved in study design, accrual, or analyses of data. The study was approved by the responsible ethical committees and medical agencies in both countries, and all patients provided written informed consent. The study is registered with ClinicalTrials.gov (NCT 00755573).

*Abbreviations used in this paper:* BPI, Brief Pain Inventory; CI, confidence interval; CNS, central nervous system; CP, chronic pancreatitis; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PDQ, Pain Detect Questionnaire; PGIC, Patients' Global Impression of Change; VAS, visual analogue scale.


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### Patients

Inclusion criteria were a diagnosis of CP based on the Mayo Clinic diagnostic criteria and chronic abdominal pain typical for pancreatitis (ie, dull epigastric pain more than 3 days per week for at least 3 months).[14] Patients taking concomitant analgesic medication and expected to stay on a stable regimen during the trial were allowed to enter the study. Key exclusion criteria for patients were generalized painful conditions other than CP, pregnancy or lactation, active (or history of) major depression, moderate to severe renal impairment, an abnormal electrocardiogram at screening, and hypersensitivity to pregabalin or any of its components.

### Randomization and Blinding

Patients meeting eligibility criteria were randomly assigned in a 1:1 ratio to receive either pregabalin or placebo. Randomization blocks had a size of 6 and were computer generated by a pseudo-random code. Trial participants were stratified according to absence or presence of diabetes mellitus; no other actions were taken to match the groups. Pfizer donated pregabalin and identical capsules containing placebo. Patients and those administrating study medication, assessing outcomes, and analyzing data were blinded to group assignment.

### Outcomes

The primary end point was change in pain intensity after 3 weeks of study treatment versus baseline pain intensity recorded for 1 week before start of medication. Average and maximum daily pain intensities were recorded using a pain diary based on a visual analogue scale (VAS) where 0 = no pain and 10 = worst pain imaginable. Secondary efficacy parameters were Patients' Global Impression of Change (PGIC) score at the end of the study period[15] and changes in modified Brief Pain Inventory-Short Form (BPI) questionnaire scores.[16] The BPI is a 14-item questionnaire that asks patients to rate pain during the prior week and the degree to which it interferes with daily activities on a 0 to 10 scale. It can be summarized in a pain composite score and an interference composite score.[16,17] Furthermore, changes in quality of life assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and tolerability of pregabalin compared with placebo were considered as secondary end points.[18] Changes in as-needed opioid analgesics (daily morphine-equivalent doses) and body mass index were collected as exploratory end points.

### Procedures

Screening procedures included a detailed patient history to determine pain localization and characteristics. To complement pain characterization, the Pain Detect Questionnaire (PDQ) was conducted. This constitutes a simple screening tool to predict the likelihood of a neuropathic pain component being present in individual patients.[19] Patients' pain medication history was documented in detail, including amount and frequency of any analgesics. Also, a physical examination, including measurement of weight, height, full blood count, urea, electrolytes, liver function tests, and electrocardiography, was performed at the screening visit. Eligible patients completed the BPI and QLQ-C30 questionnaires and were trained in the use of the pain diary. Patients returned for an enrollment visit 1 week after screening. During this visit, pain diaries were reviewed to ensure correct registration of baseline pain scores, information on analgesics was reassessed, and patients were instructed in proper administration and adjustment of the study medication. All patients received their initial dose of study drug and were monitored for 60 minutes for adverse events.

During the study period, patients received increasing doses of either pregabalin or matching placebo. The initial dose was 75 mg pregabalin twice daily. After 3 days, this was increased to 150 mg pregabalin twice daily, with a further increase to 300 mg twice daily after 1 week and for the rest of the study period. An equivalent regimen was followed in the placebo arm. All patients followed the same oral dosing schedule. Daily dosages were split into 2 equivalent doses, one administered in the morning between 7 AM and 10 AM and one in the evening between 7 PM and 10 PM. If unacceptable side effects were experienced by the



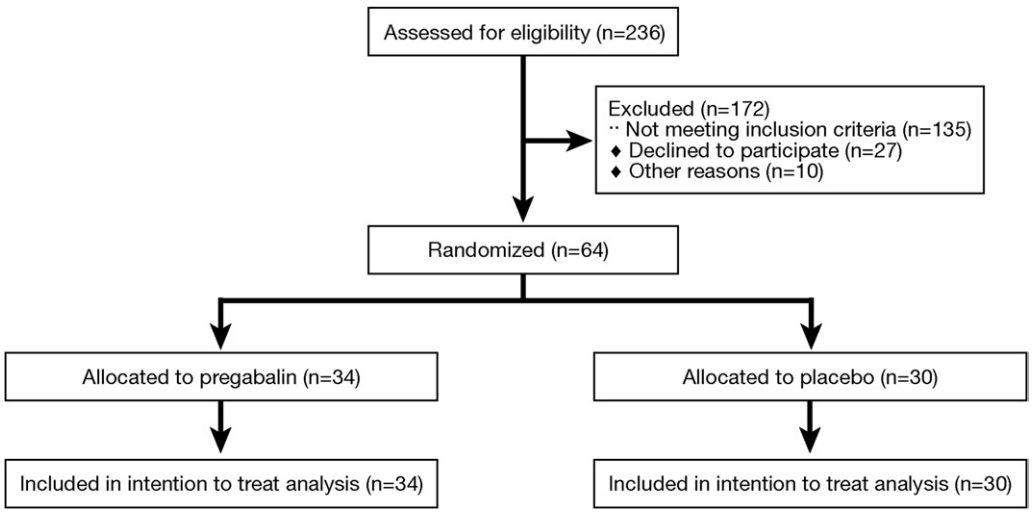


**Figure 1.** Study enrollment and randomization.

**Table 1.** Demographic and Clinical Characteristics of Patients at Randomization

| | Pregabalin (n = 34) | Placebo (n = 30) |
|---|---|---|
| Age (*y*) | 52 ± 10 | 55 ± 12 |
| Male, n (%) | 21 (62) | 19 (63) |
| Etiology, n (%) | | |
| Toxic-metabolic | 16 (47) | 17 (57) |
| Idiopathic | 11 (32) | 11 (37) |
| Genetic | 2 (6) | 0 (0) |
| Autoimmune | 1 (3) | 0 (0) |
| Recurrent and severe acute pancreatitis | 2 (6) | 1 (3) |
| Obstructive | 2 (6) | 1 (3) |
| Diary pain score (visual analogue scale 0–10) | | |
| Average pain | 4.2 ± 2.2 | 3.9 ± 2.2 |
| Maximal pain | 5.8 ± 2.3 | 5.2 ± 2.3 |
| BPI | | |
| Pain score | 4.4 ± 2.2 | 4.1 ± 2.1 |
| Interference score | 4.7 ± 2.1 | 4.6 ± 1.7 |
| PDQ | | |
| Neuropathy unlikely, n (%) | 19 (56) | 10 (33) |
| Neuropathy possible/likely, n (%) | 15 (44) | 20 (67) |
| Concomitant analgesics, n (%)[a] | | |
| None | 3 (9) | 2 (7) |
| Weak analgesics | 7 (21) | 11 (37) |
| Strong analgesics | 24 (71) | 17 (57) |
| Duration of chronic pancreatitis (*mo*) | 103 ± 75 | 111 ± 83 |
| Diabetes mellitus, n (%) | 10 (29) | 10 (33) |
| Previous interventions for chronic pancreatitis, n (%) | | |
| Pancreas resection/drainage procedures | 6 (18) | 5 (17) |
| Thoracoscopic splanchnic denervation | 2 (6) | 4 (13) |
| Celiac blockade | 1 (3) | 1 (3) |
| Patients treated with enzymes for pancreatic exocrine insufficiency, n (%) | 18 (53) | 13 (43) |
| Ongoing alcohol abuse, n (%)[b] | 7 (21) | 11 (37) |
| Current smoker, n (%) | 26 (76) | 22 (73) |
| Body mass index | 22.2 ± 5.7 | 22.5 ± 3.1 |

NOTE. Values are means ± SD. BPI denotes Brief Pain Inventory Short Form and PDQ denotes Pain Detect Questionnaire. Percentages may not total 100 due to rounding.

[a]Weak analgesics were defined as NSAIDS, paracetamol, codeine, and tramadol. Strong analgesics were defined as opioid-based therapies.

[b]Alcohol abusing patients were defined as female patients drinking >14 units of alcohol per week or male patients drinking >21 units of alcohol per week.

patient, a single downward dose titration was allowed, with the patient staying on that final dosage for the remaining study period. Telephone interviews were scheduled at 4, 7, 11, 14, and 17 days to assess the presence, severity, and tolerability of adverse events. These were collected based on their occurrence and documented in individual case report forms. After completion of the 3-week study period, patients were seen for a final visit, which included change in measurements as described for screening and the PGIC questionnaire. At the final visit, patients were instructed to taper their study medication by halving their dose for 7 days and then to stop medication.

Patients were told to return surplus study medication. Any discrepancy in the number of pills returned from the expected number of pills to be used was noted in the patient's case report form. Compliance was calculated as this discrepancy divided by the number of pills expected to be used by the individual patient.

### *Statistical Analysis*

The study was powered to detect a difference in average daily pain scores of 25% between groups during the 3 weeks of study treatment. On the basis of an assumed baseline average pain score of 4 and an SD of 30%, we determined that a study with 30 patients per group was needed to provide a power of 90% with the use of a 2-sided significance level of 0.05. Hence, the sample size was set at 64 patients to allow for possible dropouts.

All data were analyzed according to the intention-to-treat principle. Data are presented as means ± SD unless otherwise indicated. Pain diary data were baseline corrected to offset individual differences in baseline pain scores. The retrieved changes were transformed to a relative scale (%) and subjected to analysis of variance with the factors study treatment (pregabalin vs placebo) and study days (days 1–21) and the interaction of these factors. Wald tests were used for post hoc analysis. Changes in tabulated data were given as risk ratios and compared by a $\chi^2$ test or Fisher exact test as appropriate. To examine the correlation between change in diary pain score and PGIC, we used the Pearson product-moment correlation coefficient. Changes in BPI scores, QLQ-C30 scales or items, as-needed opioid analgesics, body mass index, and compliance were compared by Student *t* test or Mann–Whitney test as appropriate. The software package Stata/IC version 11.1 (StataCorp LP, College Station, TX) was used for the statistical analyses.

## Results

### *Enrollment, Baseline Characteristics, and Study Treatments*

From October 2008 to May 2010, a total of 236 patients were screened and 64 underwent randomization (Figure 1). The study was terminated as planned after randomization of 64 patients. The 2 treatment groups were comparable with respect to demographic characteristics, clinical data, and baseline pain scores (Table 1). In the pregabalin group, 20 patients (61%) tolerated a final dose of 600 mg pregabalin; in the placebo group, 26 patients (90%) tolerated the maximal placebo dose ($P = .01$).

### *Outcomes*

Changes in primary and secondary end points are summarized in Table 2. For the whole treatment period, an overall difference in change of average pain score between pregabalin- and placebo-treated patients was evident ($F = 8.8$, $P = .003$). Post hoc analysis revealed a significant difference in pain reduction after 3 weeks of study treatment (36% vs 24%; mean difference, 12%; 95% confidence interval [CI], 22% to 2%; $P = .02$) (Figure 2). In addition, an overall difference in change of maximal pain scores was seen for the whole treatment period ($F = 8.9$, $P = .003$), with a significant difference between groups after 3 weeks (32% vs 22%; mean difference, 10%; 95% CI, 19% to 2%; $P = .02$).

**Table 2.** Changes in Primary and Secondary End Points After Three Weeks of Study Treatment

| Variable | Pregabalin (n=34) | Placebo (n=30) | Pregabalin vs placebo | *P* value |
|---|---|---|---|---|
| Average diary pain score | −36% (−43%–−29%) | −24% (−31%–−16%) | −12% (−22%–−2%) | .02 |
| Maximal diary pain score | −32% (−38%–−26%) | −22% (−28%–−16%) | −10% (−19%–−2%) | .02 |
| PGIC | | | | |
| Very much improved | 1 (3) | 2 (7) | | .048 |
| Much improved | 13 (41) | 4 (14) | | |
| Minimally improved | 8 (25) | 7 (24) | | |
| No change | 7 (22) | 11 (38) | | |
| Minimal worse | 0 (0) | 4 (14) | | |
| Much worse | 2 (6) | 1 (3) | | |
| Very much worse | 1 (3) | 0 (0) | | |
| BPI | | | | |
| Pain score | −1.2 (−2.2–−0.2) | −0.4 (−1.1–−0.4) | −0.8 (−2.0–−0.4) | .19 |
| Interference score | −1.3 (−2.2–−0.3) | −1.0 (−1.7–−0.2) | −0.3 (−1.5–−0.9) | .61 |

NOTE. Pain diary data were available for 33 patients (97%) in the pregabalin group and 29 patients (97%) in the placebo group; 2 patients in the pregabalin group left the study after 11 days and 18 days; their data were included until then. Patients' global impression of change (PGIC) and brief pain inventory short form (BPI) were available for 29 patients (97%) in the placebo group. In the pregabalin group, PGIC data were available for 32 patients (97%) and BPI data for 31 patients (94%). Changes in pain diary data and BPI scores are reported as mean changes (95% confidence interval). PGIC is reported as numbers (%).

More patients rated their treatment response (PGIC) as much or very much improved in the pregabalin group (44%) compared with the placebo group (21%) ($P = .048$). The changes in average pain diary scores were correlated with PGIC scores for both the pregabalin group ($r = 0.7$, $P < .001$) and placebo group ($r = 0.5$, $P = .002$). No differences between treatments were seen for the BPI composite scores.

Changes in QLQ-C30 subscales and items are summarized in Table 3. An increase in quality of life of 9.7 points was observed in the pregabalin group compared with a decrease of 1.7 points in the placebo group ($P = .12$). No differences were seen for any of the other QLQ-C30 subscales or items.

An average reduction in as-needed opioid analgesics of 30 mg was observed in the pregabalin group compared with a reduction of 4 mg in the placebo group ($P = .02$). The average body mass index increased 0.5 kg/m$^2$ in the pregabalin group and decreased 0.2 kg/m$^2$ in the placebo group ($P < .001$).

### *Adverse Events*

During the study period, 4 patients (12%) in the pregabalin group and 2 patients (7%) in the placebo group had a serious adverse event ($P = .7$). Two patients in the placebo group and one patient in the pregabalin group were admitted to the hospital due to worsening of abdominal pain. They were treated with additional opioids as rescue medication to reduce pain. One patient receiving pregabalin had pneumonia during the downward taper medication period after the end of the study, one patient receiving pregabalin injured his shoulder in the swing door at the hospital (screening visit; ie, no study drug administered), and one patient receiving pregabalin experienced worsening of eczema during the trial.

In the pregabalin group, 35% of patients reported a feeling of being drunk compared with 7% in the placebo group ($P = .007$). Light-headedness was reported by 24% in the pregabalin group compared with 3% in the placebo group ($P = .03$). Taken together, these significant central nervous system (CNS)-related adverse effects were present in 29% of patients not taking opioids compared with 52% of patients treated with opioid analgesics ($P = .4$). Patients with CNS-related side effects used on average 146 ± 124 mg of morphine per day compared with 92 ± 139 mg in the group not experiencing CNS-related side effects ($P = .23$). All other adverse events were comparable between groups. Two patients from the pregabalin group stopped the study medication before the end of the study period due to adverse events (confusion and dizziness), and no other patients withdrew the study. Detailed information on adverse events is given in Table 4.

### *Compliance*

In the placebo group, 97% ± 5% of all study medication was taken correctly compared with 91% ± 17% in the pregabalin group ($P = .4$). The number for the pregabalin group envelopes 2 patients with poor compliance (<50%), of whom one was withdrawn from the study due to side effects (see Adverse Events).

## Discussion

Our study shows the efficacy and tolerability of pregabalin as an adjuvant analgesic for the treatment of pain caused by CP. A dosage of pregabalin between 150 and 300 mg twice daily resulted in clinically significant reductions in pain. Entries in daily pain diaries indicated that differences between pregabalin therapy and placebo were apparent 3 weeks after the first medication administration. The majority of adverse events that were reported by patients taking pregabalin, including feeling of being drunk and light-headedness, were mild to moderate in severity.

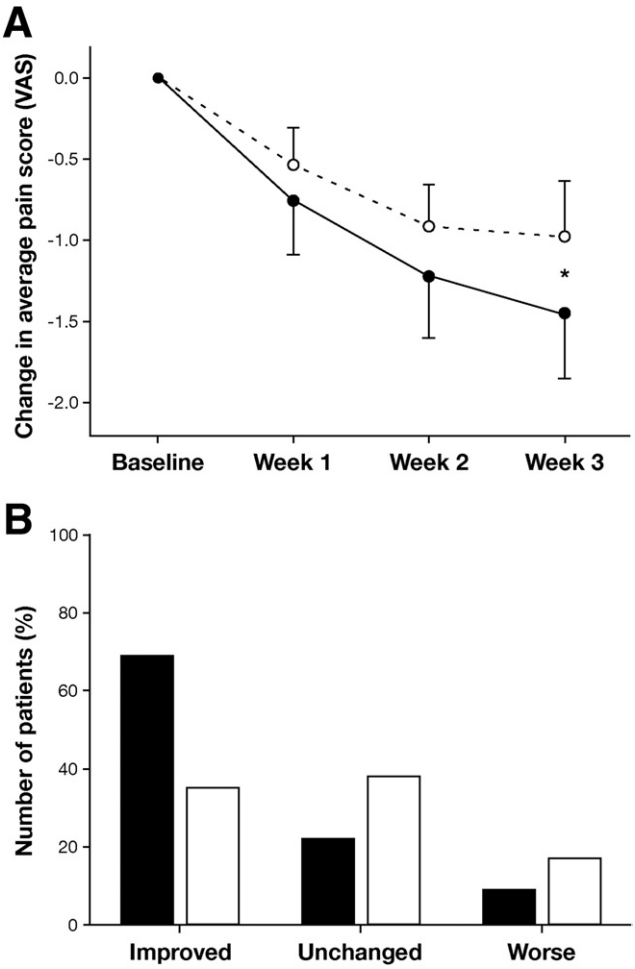


**Figure 2.** Primary and secondary outcomes. (*A*) Changes in average pain score (VAS). The *black circles* and *solid line* represent pregabalin-treated patients, and the *white circles* and *dashed line* represent patients receiving placebo. *Bars* are standard errors. $^{*}P = .02$ comparing pregabalin and placebo. (*B*) PGIC at the end of the study. *Black bars* represent pregabalin-treated patients, and *white bars* represent patients receiving placebo. There was a better treatment response in the pregabalin group ($P = .048$).

As far as we are aware, there are no published studies to date describing the use of pregabalin for pain in patients with CP. A pain reduction of 36% was seen in the pregabalin group after 3 weeks of study treatment. Several studies have examined the clinical importance of changes in chronic pain as assessed by a VAS, and reductions in chronic pain intensity of more than 30% appear to reflect at least moderately important clinically relevant differences.[15,20] The clinical importance of the observed pain reduction was further supported by the association with self-reported health status (PGIC).[15] Comparable findings have been reported from randomized controlled trials in diabetic polyneuropathy, postherpetic neuralgia, and central neuropathic pain, where maximal analgesic effects were seen after 2 weeks of treatment.[8,10,11,13] Also, these findings are in agreement with a recently published meta-analysis in which the efficacy and adverse effects of pregabalin were determined for various neuropathic pain disorders.[9]

The extensive placebo response (24%) seen in the present study was unexpected. In most pregabalin trials, a placebo response of less than 10% has been reported.[8,10,11,13] A large pain reduction in the group receiving placebo may mask the genuine efficacy of pregabalin.[9] It is most likely that this phenomenon explains the discrepancy between the expected effect of 25% pain reduction between groups and the retrieved effect of 12%.

CNS adverse effects were experienced by a number of patients in the pregabalin group, with an incidence comparable to previous studies of gabapentoids.[9] The adverse effects were mild to moderate in severity and, as seen in the clinic and in previous reports, declined to a tolerable level during the course of the trial for most patients.[9] This was illustrated by the fact that only 2 patients had to stop pregabalin treatment before the end of the study period. Furthermore, two-thirds of patients in the pregabalin group rated their global health score as improved after pregabalin treatment, thus emphasizing beneficial analgesic effects over adverse effects for most patients. Patients should, however, be informed of potential CNS side effects before the start of pregabalin treatment, including a feeling of being drunk and light-headed, dizziness, and drowsiness.

The majority of patients in the current study were treated with opioids, and one-fourth of patients (n = 19) had undergone interventional therapies for CP pain. Despite these aggressive treatment approaches, patients still had severe pain at enrollment. Hence, the study population was at the lower end of the treatment algorithm suggested by the American Gastroenterological Association guidelines and thus comprised a patient group that is very difficult to treat.[1] In light of this, the observed treatment response is considered clinically relevant.

The rationale for the present study was based on the hypothesis that the alterations in peripheral and central pain processing underlying pain in patients with CP resemble those accompanying neuropathic pain. Thus, enhanced neural density and hypertrophy of pancreatic nerves along with up-regulation of pro-nociceptive mediators in the pancreatic gland were previously reported in patients with CP.[7,21] In addition, widespread or generalized hyperalgesia has been shown in CP pain, along with cortical reorganization and impairments of descending inhibitory control mechanisms, suggesting the presence of aggressive central sensitization in these patients.[4,6,22,23] Taken together, these alterations are similar to those accompanying neuropathic pain and respond poorly to traditional opioid-based approaches.[24,25] On the contrary, gabapentinoids, such as pregabalin, have been shown to be successful in treating pain associated with such nerve damage and hyperalgesia.[9,26]

As suggested by the current guidelines from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT recommendations), we used several outcome measures to assess the efficacy of pregabalin.[20,27] By using a multidimensional test battery, the complex nature of pain can be explored and associations

**Table 3.** Changes in EORTC QLQ-C30 Questionnaire Scales and Items

| Variable | Pregabalin (n=34) | Placebo (n=30) | Pregabalin vs placebo | *P* value |
|---|---|---|---|---|
| Global health status (quality of life) | 9.7 (−0.5–19.9) | −1.7 (−12.4–8.9) | 11.4 (−3.0–25.8) | .12 |
| Functioning scales | | | | |
| Physical functioning | 0.2 (−7.0–7.4) | −2.0 (−8.6–4.6) | 2.2 (−7.4–11.8) | .65 |
| Role functioning | 2.2 (−9.6–14.0) | 1.7 (−9.7–13.1) | 0.5 (−15.6–16.6) | .95 |
| Emotional functioning | 6.7 (−2.8–16.1) | 5.4 (−3.7–14.4) | 1.3 (−11.5–14.1) | .84 |
| Cognitive functioning | 4.8 (−4.4–14.1) | 5.2 (−5.0–15.4) | −0.3 (−13.8–13.1) | .96 |
| Social functioning | 11.5 (−2.3–25.3) | 16.1 (4.3–27.8) | 4.6 (−22.3–13.2) | .61 |
| Symptom scales/items | | | | |
| Fatigue | −12.2 (−23.8–−0.6) | 2.4 (−9.5–14.3) | −14.6 (−30.9–1.7) | .08 |
| Nausea and vomiting | −7.0 (−15.6–1.6) | 0.0 (−11.0–11.0) | −7.0 (−20.5–6.6) | .31 |
| Pain | −17.2 (−30.3–−4.1) | −4.0 (−16.7–8.6) | −13.2 (−31.0–4.7) | .14 |
| Dyspnea | −2.2 (−9.8–5.5) | −4.6 (−13.4–4.2) | 2.4 (−8.9–13.8) | .67 |
| Insomnia | −18.3 (−33.4–−3.2) | −13.8 (−30.6–3.0) | −4.5 (−26.5–17.5) | .69 |
| Appetite loss | −18.9 (−34.0–−3.7) | −18.4 (−33.8–−3.0) | −0.5 (−21.7–20.7) | .96 |
| Constipation | −1.1 (−16.0–13.9) | 4.6 (−6.5–−15.7) | −5.7 (−24.1–12.8) | .54 |
| Diarrhea | −7.5 (−14.4–0.7) | 0.0 (−10.7–10.7) | −7.5 (−19.8–4.7) | .22 |
| Financial difficulties | −12.9 (−23.7–−2.1) | −13.8 (−27.6–0.0) | 0.9 (−16.1–17.9) | .92 |

NOTE. QLQ-C30 data were available for 31 patients (94%) in the pregabalin group and for 29 patients in the placebo group (97%). Changes in subscales or items are reported as mean changes (95% confidence interval).

between quantifiable outcomes (such as changes in pain diary scores) can be associated with changes in qualitative outcomes (such as PGIC), and thereby a comprehensive multidimensional impression of the clinical importance of the analgesic efficacy may be obtained. We closely monitored patients using telephone interviews every third day throughout the study period to accurately document side effects and permit dose adjustment in case unacceptable adverse effects were experienced. This approach may explain the good trial adherence, with only 2 patients leaving the study before the end of the trial period due to side effects.



**Table 4.** Adverse Events During the Study Period

| | | n *(%)* | | | |
|---|---|---|---|---|---|
| | Event | Pregabalin (n=34) | Placebo (n=30) | Risk ratio (95% CI) | *P* value |
| | Any adverse event | 31 (91) | 16 (53) | 1.7 (1.2–2.4) | .001 |
| Central nervous system | Feeling drunk | 12 (35) | 2 (7) | 5.3 (1.3–21.8) | .007 |
| | Mild/moderate/severe | 4/7/1 | 0/2/0 | | |
| | Light-headedness | 8 (24) | 1 (3) | 7.1 (0.9–53.2) | .03 |
| | Mild/moderate/severe | 6/2/0 | 1/0/0 | | |
| | Dizziness | 13 (38) | 5 (17) | 2.3 (0.9–5.7) | .09 |
| | Drowsiness | 12 (35) | 6 (20) | 1.8 (0.8–4.1) | .27 |
| | Trouble concentrating | 3 (9) | 1 (3) | 2.6 (0.3–24.1) | .62 |
| | Headache | 4 (12) | 4 (13) | 0.9 (0.2–3.2) | 1.00 |
| | Amnesia | 2 (6) | 0 (0) | — | .49 |
| | Migraine attack | 1 (3) | 0 (0) | — | 1.00 |
| | Myoclonus | 2 (6) | 0 (0) | — | .49 |
| | Tremor | 1 (3) | 0 (0) | — | 1.00 |
| Gastrointestinal/ metabolic | Dry mouth | 4 (12) | 0 (0) | — | .12 |
| | Worsening of abdominal pain | 3 (9) | 4 (13) | 0.7 (0.2–2.7) | .70 |
| | Nausea and vomiting | 3 (9) | 6 (20) | 0.44 (0.1–1.6) | .28 |
| | Decreased glucose tolerance | 1 (3) | 0 (0) | — | 1.00 |
| Musculoskeletal | Muscle cramp | 0 (0) | 1 (3) | — | .47 |
| | Back pain | 1 (3) | 1 (3) | 0.9 (0.1–13.5) | 1.00 |
| | Injured shoulder | 1 (3) | 0 (0) | — | 1.00 |
| Other | Urine retention | 1 (3) | 0 (0) | — | 1.00 |
| | Change in sexual function | 2 (6) | 0 (0) | — | .49 |
| | Blurred vision | 2 (6) | 0 (0) | — | .49 |
| | Pneumonia | 1 (3) | 0 (0) | — | 1.00 |
| | Worsening of eczema | 1 (3) | 0 (0) | — | 1.00 |

There are important limitations to this study. First, the follow-up period of 3 weeks is likely too short to detect changes in functional scales and quality of life. Whether an effect would have been detected on these parameters if the study period was prolonged is unknown, although studies with longer observation periods have reported an improved quality of life in patients with neuropathic pain who were treated with pregabalin.[8,10,13] Second, the fact that only half of patients had alcohol abuse as a cause of CP may compromise the external validity of the study. In northern Europe, two-thirds of patients with CP have alcohol abuse as the leading cause of CP.[28] Third, it would have been of great interest to compare the effects of pregabalin between patients with and without previous pancreatic surgery. However, only one-fifth of patients (n = 11) had previous surgery for pain. Therefore, the study is unlikely to be powered for a subanalysis with stratification on previous surgery. Fourth, the PDQ questionnaire was originally developed and validated in somatic pain (patients with lower back pain) and has never been validated for assessment of visceral pain.[19] Consequently, it may be questioned whether the PDQ is valid for documentation of neuropathic pain in patients with CP and future studies are awaited to answer this question. For these reasons, the number of patients with neuropathy documented by the PDQ at baseline should be interpreted with caution. Finally, this study does not assess whether pregabalin is suitable for use as a first-line analgesic for treatment of pain in CP. This important clinical question should be explored in a future head-to-head study comparing pregabalin with standard analgesics such as opioids and/or interventional treatments. Further studies will also be necessary to document whether pregabalin improves quality of life for patients with CP pain.

Our study provides evidence that the adjuvant administration of pregabalin for the treatment of pain in patients with CP is superior to placebo. The side effects reported in the pregabalin group were moderate and in general well tolerated. In conclusion, pregabalin can be used in combination with other analgesics or interventional therapies to obtain better control of the disabling pain in CP.



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*Conflicts of interest*

The authors disclose no conflicts.

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