Original Article

Prolonged Treatment with Transdermal Fentanyl in Neuropathic Pain

Paul L. I. Dellemijn, MD, PhD, Hans van Duijn, MD, PhD, and Jan A. L. Vanneste, MD, PhD
Departments of Neurology and Clinical Neurophysiology (P.L.I.D., H.v.D., J.A.L.V.), Saint Lucas Andreas Hospital, Amsterdam, The Netherlands, and Departments of Neurology and Clinical Neurophysiology (P.L.I.D.), Saint Joseph Hospital, Veldhoven, The Netherlands

Abstract
Forty-eight patients with noncancer neuropathic pain who had participated in a randomized controlled trial with intravenous fentanyl (FENiv) infusions received prolonged transdermal fentanyl (FENtd) in an open prospective study. Pain relief, side effects, tolerance, psychological dependence, mood changes, and quality of life were evaluated. The value of clinical baseline characteristics and the response to FENiv also was evaluated in terms of the outcome with long-term FENtd. Eighteen patients stopped prematurely because of insufficient pain relief, side effects, or both. Among the remaining 30 patients completing the 12-week dose titration protocol, pain relief was substantial in 13 and moderate in five. Quality of life improved (23%, P < 0.01). Psychological dependence or the induction of depression was not observed. In only one patient did tolerance emerge. There was a significant positive correlation between the pain relief obtained with FENiv and that with prolonged FENtd (r = 0.59, P < 0.0001). We conclude that (1) long-term transdermal fentanyl may be effective in noncancer neuropathic pain without clinically significant management problems and (2) a FENiv-test may assist in selecting neuropathic pain patients who might benefit from prolonged treatment with FENtd.


Key Words
Pain, neuropathic pain, drug treatment, opioids, fentanyl, transdermal delivery, cutaneous, side effects, quality of life, clinical trial

Introduction
Treatment of noncancer neuropathic pain is often disappointing.1,2 When neuropathic pain is resistant to commonly used drugs, an opioid trial may be justified.3–8 Prolonged opioid therapy for severe nonmalignant neuropathic pain remains a matter of debate because of concerns about efficacy, psychological dependence, illicit use, tolerance, side effects, and the lack of concomitant psychological and functional improvement.4,8–16

We have shown that intravenous infusions with the opioid fentanyl (FEN) may produce substantial pain relief in 58% of patients with nonmalignant neuropathic pain.17 The present study was undertaken to (1) assess whether transdermal fentanyl (FENtd) may lead to persistent pain relief in patients with neuropathic pain.
pain, (2) assess the severity and impact of side effects of prolonged FENtd treatment, and (3) study whether a fentanyl infusion test might assist the clinician in selecting patients for long-term fentanyl therapy.

**Methods**

**Patients**

Subjects with noncancer neuropathic pain were recruited from our own outpatient clinic population and through telephone requests and letters to colleagues from Amsterdam and surroundings who were presumed to treat patients with neuropathic pain, such as neurologists, neurosurgeons, and anesthesiologists. All patients who completed a randomized, double-blind, active placebo-controlled trial with intravenous infusions of either FEN and diazepam or FEN and saline were invited to be enrolled in this second study assessing the benefits and risks of prolonged treatment with FENtd.

Inclusion criteria included continuous non-cancer neuropathic pain [defined as pain along the course of one or more peripheral nerve(s), nerve root(s), or pain over a delineated skin area served by nerve(s), nerve root(s) or a part of the central nervous system, with corresponding somatosensory dysfunction], age 18–75 years, ability to rate the pain on a 0–100 numerical rating scale (NRS) and quality of life on a 0–100 mm visual analogue scale (VAS), pain intensity of ≥ 40 mm on a 100 mm VAS, and written informed consent.

Exclusion criteria were use of opioids or modified drug regimens during the 2 weeks before starting the study; contraindications to opioids, such as a history of opioid abuse; presence of multiple sites or other types of pain; intermittent neuropathic pain, such as trigeminal neuralgia; and uncertainty about the neuropathic origin of pain.

Neuropathic pain was classified as (1) nociceptive nerve (root) pain when the pain was perceived along the course of a nerve root with evidence of active nerve inflammation, for example, acute radicular pain due to disc protrusion; (2) deafferentation pain when there was pain in a delineated skin area with signs of sensory dysfunction and evidence of damage in a corresponding part of the central or peripheral nervous system, but without evidence of inflammation, for example, postherpetic neuralgia, phantom pain, posttraumatic neuralgia, central pain, post-rhizotomy pain; and (3) mixed neuropathic pain when both nociceptive nerve and deafferentation pain were possibly involved, for example, chronic radicular pain associated with a failed back surgery syndrome.

The baseline assessment consisted of a standardized medical history and neurological examination, which included a thorough examination on the area of sensory dysfunction. A nonquantitative sensory examination of pain perception to pin prick, cold sensation to a cooled (5°C) metal disc, and mechanical touch to a moving cotton swab over the skin was carried out on the painful side and compared with the corresponding area of the nonpainful side. Quantitative sensory assessment in the center of the above mentioned area(s) consisted of studying the thresholds to (1) mechanical stimulation with von Frey hairs, (2) warm and cold detection, and (3) heat and cold pain, as previously described. Types and degrees of disturbed sensation were registered and included hyperpathia, hypo- and hyperalgasia to pin-prick, mechanical hypoesthesia and allodynia, cold and warm hypoesthesia, cold and heat pain hyperalgesia (results have been reported elsewhere).

Patients rated their actual pain intensity (PI) and pain unpleasantness (PU) daily on a 0–100 NRS at rest and at a fixed time. The difference between sensory and affective dimensions of pain was explained by telling a standard story containing examples illustrating this difference. The severity of depression was assessed with a Dutch validated version of the Zung depression scale (ZDS). A score of 25–35 signified no depression; 36–50: moderate depression; and 51–100: marked depression. Quality of life was assessed with a validated quality of life index (QLi), a global score consisting of 13 items and subdivided in three subfactors: Factor 1 (F1) assessed symptom control: pain and side effects such as nausea and vomiting. Factor 2 (F2) assessed physical well-being: appetite, eating, working, strength, and sex. Factor 3 (F3) assessed psychological well-being: satisfaction, general quality of life, usefulness, and sleep.

**Drug Administration**

The dose of FENtd was individually titrated during 12 weeks in order to obtain an optimal
relief of PI and PU. The consecutive doses were 25, 50, 75, and 100 µg FEN/hr [fentanyl-transdermal therapy system (TTS), Durogesic™, Janssen-Cilag]. Treatment was always started with 25 µg FEN/hr and titrated upward when pain intensity had not decreased to 25% of baseline pain intensity after 2 weeks. The dose was increased to the highest tolerable dose with a maximum of 100 µg FEN/hr. Vomiting was treated symptomatically or, if necessary, by lowering the dose of FENtd. After 12 weeks of treatment the dose was tapered with 25 µg/hr weekly, eventually stopped, and substituted by 60 mg sustained-release morphine/day. Oral morphine was tapered from 60 mg/day to 0 mg within 10 days. After a washout period of 2 weeks, the opportunity of resuming treatment with FENtd was offered to all patients who completed this protocol, and they were asked to account for their choice: either resuming FENtd because of satisfactory pain relief and/or other reasons, or not resuming FENtd because of unsatisfactory pain relief, side effects, other reasons, or a combination of these factors. Other analgesics and adjuvant drugs that had been part of the patient’s therapy were continued at the same dose level throughout the clinical trial.

Evaluation
The degree of PI difference (PID) was calculated as the mean PI (7 daily scores) during baseline (week 0) before starting FENtd minus the mean PI of each of the 12 treatment weeks with FENtd or the second opioid-free week after washout. The PID was expressed as a percentage of baseline PI: %PID = (PID/baseline PI) × 100. PU difference (PUD) was calculated in a similar way: %PUD = (PUD/baseline PU) × 100. Both maximal %PID (%PID_max) during the least painful week and average %PID (%PID_av) were calculated for FENtd in all patients, in order to assess whether %PID_max was an incidental improvement or not. To evaluate the clinical efficacy of FENtd, we also transformed the data on %PID after 12 weeks of FENtd treatment (%PID_{T_12W}) to a nominal scale (grade 1, %PID_{T_12W} < 25%; grade 2, 25% ≤ %PID_{T_12W} < 50%; grade 3, %PID_{T_12W} ≥ 50%). Tolerance was defined as the need for increasing the dose of FENtd due to pain increase of at least one grade, after substantial pain relief (grade 3) during at least 2 weeks with a fixed dose of FENtd had been obtained.

All types of side effects were noted and the severity of side effects was scored by the patient on a VAS ranging from 0 (no side effects) to 100 mm (intolerable side effects). The degree of sedation was separately assessed on a VAS ranging from 0 (normal alertness) to 100 mm (cannot stay awake).

The dose of FENtd, PI and PU, side effects and sedation were recorded daily in a pain diary. The QLi was scored weekly. ZDS was assessed at entry, at the end of the 12-week treatment, after the 2 opioid-free weeks, and after 1 year of treatment. Regular follow-up was planned as long as treatment with FENtd continued.

Statistical Analysis
The %PID and %PUD were compared with paired t-tests. Linear regression analysis was performed to evaluate the correlations (1) between %PID_{av} obtained with FENtd and with FENiv, (2) between %PID_{av} and PID_max obtained with FENtd, (3) between changes in depression scores and %PID_{T_12W}, and (4) between QLi and %PID_{T_12W}. Comparisons between the three modes of %PID (%PID_max, %PID_{av}, %PID_{T_12W}) and comparisons between subgroups were performed with t tests or Fisher’s exact test. Results were considered statistically significant at the P < 0.05 level.

Ethical Approval
The trial was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Saint Lucas Andreas Hospital.

Results
Study Population and Trial Profile
Of the 50 patients who had participated to the fentanyl infusion study, 48 accepted enrolment in this FENtd study, one refused because of persistent decrease in pain intensity and one because of fear of side effects. The baseline characteristics are listed in Table 1. The trial profile is shown in Figure 1, sixteen patients discontinued FENtd prematurely, because of unsatisfactory pain control, side effects, or both; in only one of these cases, the %PID of the last treatment week was greater
than 50%. Two patients were lost to follow-up. Of the 30 patients who completed the dose titration protocol during 12 weeks, 17 decided not to resume treatment with FENtd after the washout period. The reasons were the following: In 13, pain relief did not outweigh side effects, although pain relief was grade 3 in three patients and grade 2 in one patient. In four, substantial pain relief (grade 3) persisted after washout; in these four patients, pain had been present from 25, 16, 6, and 2 months before treatment with FENtd. The remaining 13 chose to resume FENtd, because they estimated that pain relief was satisfactory (grade 3 in eight, grade 2 in five patients) and that side effects were tolerable. Three of them discontinued FENtd during the first year, because pain relief did no longer outweigh the burden of side effects. After 2 years, nine are still using FENtd.

### Pain Relief

Data from 44 patients were analyzable for pain relief (two lost to follow-up; in two others, diaries were lost). Figure 2 shows a high correlation between \%PID\(_{\text{max}}\) and \%PID\(_{\text{av}}\) during FENtd therapy, illustrating that the week of maximal PID was not an incidental event. In Figure 3, a significant positive correlation is shown between \%PID\(_{\text{av}}\) during the FENiv test and \%PID\(_{\text{av}}\) during FENtd.

Figure 4 shows the mean \%PID and \%PUD during the 12 weeks of treatment with FENtd, and during the opioid-free observation week (OF) in the 30 FEN\(_{12w}\) patients. Individual dose titration with FENtd produced increasing and significant pain relief. No significant difference between \%PID and \%PUD was noted. Table 2 shows \%PID in the eight diagnostic groups and the three types of neuropathic pain in the 30 FEN\(_{12w}\) patients. Clinically relevant pain relief was observed for all three modes of \%PID (%PID\(_{\text{max}}\), %PID\(_{\text{av}}\), %PID\(_{12w}\)). There was no significant difference in pain relief between the group with mixed neuropathic pain and that with deafferentation pain (for example, for PID\(_{\text{max}}\): \(P = 0.49\)).

### Dosage and Tolerance

The maximal tolerated dosage of FENtd during the last treatment week was 75 μg/hr in seven patients, 50 μg/hr in 21 patients, and 25 μg/hr in 16 patients. The mean dosage at the end of treatment was similar in the 3 types of neuropathic pain. Tolerance to the analgesic effect of FENtd was not observed in any patient at the 12-weeks follow-up.

### Side Effects

Figure 5 shows the type and incidence of side effects during FENtd treatment. The most frequent side effects were sedation and nausea; constipation was seen in 36%. No serious side effects were reported by any patient.
effects, such as respiratory depression or addictive behavior, were observed. Severe withdrawal symptoms occurred in two patients who abruptly discontinued treatment without seeking advice. Figure 6 shows the decrease in the severity of side effects and sedation level after the first week of treatment with FENtd in the 30 FEN12w patients.

Quality of Life and Depression
Figure 7 illustrates that in the 30 FEN12w patients, the global QLi showed an improvement of 23% (P < 0.01), mainly due to improved psychological well-being. There was no change in mean depression scores; eight patients with marked depression became less (“moderately”) depressed and one with moderate depression became markedly depressed. There was no correlation between pain relief and depression scores or changes in QLi.

Patient Characteristics, Results of FENiv, and Treatment Effect
Table 3 shows that no baseline characteristic predicted substantial pain relief (grade 3) with FENtd. Conversely, there was a significant positive correlation between pain relief during FENiv and that obtained with FENtd. Table 4 shows that the group of 13 patients with substantial pain relief (grade 3) reported an improvement in their quality of life, mainly due to improved psychological well-being.

Prolonged Follow-Up After 2 Years
Among the nine patients still using FENtd after 2 years, pain relief is substantial (grade 3) in four, moderate (grade 2) in two, and negligible (grade 1) in three patients. Mean %PID is 47%. Improvement of the QLi is substantial (≥ 50%) in two, moderate (20%–50%) in
three, and absent in four. There was no sub-
stantial change in depression scores. The sever-
ity of side effects remained low and did not
preclude further FENtd therapy. In one pa-
tient who suffered severe deafferentation pain
in the arm due to syringomyelia, tolerance to
the analgesic effect emerged after 2 years in
spite of 100 μg/hr FENtd.

Discussion
This prospective open label study of pro-
longed treatment with the opioid fentanyl sug-
gests that substantial and sustained pain relief
may be obtained in a minority of patients with
noncancer neuropathic pain, including deaf-
ferentation pain. After 12 weeks of FENtd ad-

![Graph](image1)

**Fig. 3.** Average pain relief with FENiv test versus FENtd. Symbols: see Figure 2 (N = 44, r(PI) = 0.59, P < 0.0001)

![Graph](image2)

**Fig. 4.** Time-related pain relief with FENtd. Change in % pain-intensity (PI, black symbols) and pain-unpleasant-
ness (PU, open symbols) compared to baseline pain in the 30 patients with neuropathic pain. Error bars: 95% con-
fidence intervals; Negative scores indicate that pain increased. OF: opioid-free observation week.
ministration, 17 out of 48 (35%) patients reported satisfactory pain relief with acceptable side effects. In four of them, however, pain did not recur after wash-out of FENtd; although the pain had been present for more than a year (15 and 24 months) before starting FENtd in two of these four patients, we cannot exclude a placebo effect or spontaneous pain relief. Of the 13 who decided to continue FENtd beyond 12 weeks, 8 patients (17%) still experience satisfactory pain relief after 2 years of treatment. Insufficient pain control, sedation, and nausea were the main limiting factors precluding further dose titration.

These results are similar to those described in retrospective studies on prolonged treatment with opioids in noncancer neuropathic pain: substantial pain relief with acceptable side effects has been noted in 17%–57% of patients.3,7,24 This high variability may be due to selection biases, including the number of previous opioid-users and psychiatric disorders, the duration of follow-up, and the criteria for clinical effectiveness.4,6,7 Similarly, the high proportion of depressed women in our study may have biased our results, and precludes an informative comparison between depressed and nondepressed patients.

### Table 2

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Subgroups</th>
<th>pts</th>
<th>%PID&lt;sub&gt;max&lt;/sub&gt;</th>
<th>%PID&lt;sub&gt;av&lt;/sub&gt;</th>
<th>% PID after 12 weeks FENtd</th>
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<td>Radiculopathy</td>
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<td>Acute from disc protrusion</td>
<td>1</td>
<td>86.0</td>
<td>44.0</td>
<td>86.0</td>
<td>0</td>
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<td>Chronic from epidural fibrosis</td>
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<td>40.5</td>
<td>24.9</td>
<td>31.3</td>
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<td>Chronic idiopathic</td>
<td>6</td>
<td>38.5</td>
<td>21.8</td>
<td>32.8</td>
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<td>Posttraumatic neuralgia</td>
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<td>49.2</td>
<td>36.0</td>
<td>35.9</td>
<td>2</td>
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<td>36.1</td>
<td>23.4</td>
<td>25.0</td>
<td>1</td>
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<td>Phantom pain</td>
<td>1</td>
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<td>Central pain</td>
<td>2</td>
<td>77.4</td>
<td>45.5</td>
<td>70.0</td>
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<tr>
<td>Postrhizotomy pain</td>
<td>1</td>
<td>84.2</td>
<td>84.2</td>
<td>84.2</td>
<td>0</td>
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<tr>
<td>Nociceptive nerve pain</td>
<td>1</td>
<td>86.0</td>
<td>44.0</td>
<td>86.0</td>
<td>0</td>
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<tr>
<td>Mixed neuropathic pain</td>
<td>17</td>
<td>39.8</td>
<td>23.8</td>
<td>31.8</td>
<td>2</td>
</tr>
<tr>
<td>Deafferentation pain</td>
<td>12</td>
<td>51.7</td>
<td>37.5</td>
<td>42.1</td>
<td>3</td>
</tr>
<tr>
<td>Totals</td>
<td>30</td>
<td>45.9**</td>
<td>29.7*</td>
<td>37.6*</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

Pain relief in the 30 patients who completed the FENtd trial (12 weeks). %PID<sub>max</sub>: maximal difference of %PID; %PID<sub>av</sub>: average %PID during 12 weeks; %PID<sub>12w</sub>: %PID after 12 weeks of FENtd. Levels of significance are indicated where appropriate: *P < 0.0005; **P < 0.0001.

### Table 3

<table>
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<tr>
<th>Baseline characteristics</th>
<th>50% or more</th>
<th>less than 50%</th>
<th>P value</th>
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<tr>
<td></td>
<td>N = 13</td>
<td>N = 17</td>
<td></td>
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<tr>
<td>Baseline characteristics</td>
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<tr>
<td>Age in years</td>
<td>52.8 (46.9–58.6)*</td>
<td>46.4 (38.8–54.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/2</td>
<td>13/4</td>
<td>NS</td>
</tr>
<tr>
<td>Zung depression score</td>
<td>64.0 (59.7–68.2)</td>
<td>64.3 (59.2–69.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Quality of life on VAS</td>
<td>51.7 (45.3–59.7)</td>
<td>55.4 (45.3–61.5)</td>
<td>NS</td>
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<tr>
<td>Previous opioid use (%)</td>
<td>85.6 (64.2–105.0)</td>
<td>64.7 (41.3–88.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain duration median (range) in months</td>
<td>38 (1–146)</td>
<td>26 (2–253)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain intensity on NRS</td>
<td>68.3 (59.2–77.5)</td>
<td>65.9 (58.4–73.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain unpleasantness on NRS</td>
<td>70.4 (60.0–80.8)</td>
<td>69.9 (61.3–78.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Type of neuropathic pain mixed</td>
<td>7 (44%) vs. 5 (42%)</td>
<td>10 (50%) vs. 7 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intravenous fentanyl test</td>
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<tr>
<td>Maximum relief of pain intensity (%PID&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>82.1 (69.5–95.3)</td>
<td>51.0 (34.2–57.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Average relief of pain intensity (%PID&lt;sub&gt;av&lt;/sub&gt;)</td>
<td>60.2 (47.8–72.5)</td>
<td>29.1 (17.4–40.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Between brackets: 95% confidence intervals.
M, male; F, female; VAS, visual analogue scale; CI, confidence interval; NRS, numerical rating scale.
Relief of pain intensity and pain unpleasantness was similar, supporting our previous findings that FEN has an intrinsic analgesic effect not related to its euphoriant properties. This is in contradiction with the opinion of other investigators,\textsuperscript{4,21} who have suggested that opioids may relieve neuropathic pain mainly by influencing the affective dimension of pain perception. In those of our patients who experienced substantial pain relief, a clinically relevant improvement in the quality of life without the induction of depression was noted. This confirms the findings of other investigators,\textsuperscript{3,4,24–26} but contradicts a placebo-controlled study on the efficacy of oral morphine in chronic non-malignant pain, in which substantial pain relief was not paralleled by functional improvement.\textsuperscript{11}

Thirty-five percent of our patients discontinued the trial prematurely because of side effects, mainly sedation and nausea. In retrospect, we presume that in some patients the initial dose of FENtd had been too high: a patch delivering 25\textsuperscript{\mu}g FEN/hr is equivalent to 2–3 mg morphine/hr, which is a high starting dose. It became clear that when patients were able to cope with side effects during the 1st weeks of FENtd, gradual increase of pain relief contrasted with a simultaneous decrease of the severity of side effects, including sedation. An incidence of 36\% of constipation without prophylactic laxatives was comparable to percentages noted in other studies on long-term opioid therapy with morphine and FENtd.\textsuperscript{3,7,27}

Feared opioid-induced side effects, such as respiratory depression, the induction of severe depression, and psychological dependence were not observed. This is in accordance with other studies on opioid treatment for chronic non-malignant pain, in which a low risk of iatrogenic psychological dependence has been
observed in patients without a history of substance abuse.\textsuperscript{6,9,11,26,28,29} After 2 years, tolerance developed in only one patient. Other investigators have also shown that tolerance to the analgesic effect of opioids is rarely (0%–6%) a clinical problem.\textsuperscript{4,29,30}

Although substantial pain relief with FENiv had been obtained in 58% of the same patient group,\textsuperscript{17} only 17% continued FENtd after 2 years of treatment. Determining the predictors which would increase the pre-treatment probability of opioid responsiveness is therefore a pressing need. The baseline characteristics that we pre-selected to assess their value for predicting FEN responsiveness were not useful. These included age; sex; duration, etiology and type of neuropathic pain; the presence and severity of depression; previous opioid use; and the quality of life before starting FENtd. Conversely, quite a good correlation was found between the results of the FENiv test and the responsiveness to FENtd. In view of the unpredictability of clinical baseline characteristics, we assume that a FENiv test might contribute to a better selection of patients with neuropathic pain for prolonged therapy with FENtd. This should be confirmed by a double-blind, active placebo-controlled study, provided that this experiment proved feasible in view of the potential reticence many patients might show towards participating in a trial which included a study arm with an active placebo mimicking opioid-induced side effects.

**Acknowledgment**

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<table>
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<th>Table 4</th>
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<tr>
<td><strong>Influence of Pain Relief on Depression and Quality of Life</strong></td>
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</table>

| Treatment differences | Pain relief after 12 weeks FENtd (%PID\textsubscript{12w}) |
| --- | --- | --- |
| Change in Zung score (points) | 50% or more | Less than 50% |
| \(N = 13\) | \(N = 17\) | \(P\) value |
| 6.0 (–0.58 – 12.4)\textsuperscript{*} | 1.1 (–4.13 – 6.35) | NS |
| Change in global QLi (mm VAS) | 19.5 (6.1 – 32.8) | –2.7 (–13.2 – 7.9) |
| Factor 1: symptom control | 12.3 (2.3 – 22.9) | 2.0 (–8.1 – 12.1) |
| Factor 2: physical well-being | 14.6 (–0.59 – 29.8) | –7.4 (–22.1 – 7.3) |
| Factor 3: psychological well-being | 32.4 (9.7 – 55.1) | –0.5 (–14.7 – 13.7) | 0.02 |

\textsuperscript{*}Between brackets: 95% confidence intervals. QLi: quality of life index; Factor 1,2,3: subfactors of QLi, see methods. VAS, visual analogue scale.
References


