Original Article

Prolonged Treatment with Transdermal Fentanyl in Neuropathic Pain

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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. J Pain Symptom Manage 1998;16:220–229. *© U.S. Cancer Pain Relief Committee, 1998.*

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

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Accepted for publication: January 30, 1998.

Published by Elsevier, New York, New York

0885-3924/98/$19.00
PII S0885-3924(98)00070-0

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[17] were invited to be enrolled in this second study assessing the benefits and risks of prolonged treatment with FENtd.

Inclusion criteria included continuous noncancer 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[18]], 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 $\geq$ 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.[19] Types and degrees of disturbed sensation were registered and included hyperpathia, hypo- and hyperalgesia to pin-prick, mechanical hypoesthesia and allodynia, cold and warm hypoesthesia, cold and heat pain hyperalgesia (results have been reported elsewhere).[20]

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.[21] The severity of depression was assessed with a Dutch validated version of the Zung depression scale (ZDS).[22] 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),[23] 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 ($\%PID_{12w}$) to a nominal scale (grade 1, $\%PID_{12w} < 25\%$; grade 2, $25\% \leq \%PID_{12w} < 50\%$; grade 3, $\%PID_{12w} \geq 50\%$). 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 $\%PID_{12w}$, and (4) between QLi and $\%PID_{12w}$. Comparisons between the three modes of %PID ($\%PID_{max}$, $\%PID_{av}$, $\%PID_{12w}$) and comparisons between subgroups were performed with *t* tests or Fisher's exact test. Results were considered statistically significant at the *P* less than 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,[17] 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

Table 1
Baseline Characteristics of 48 Patients Enrolled in the FENtd Study

Age in years	
Mean (range)	49 (21–75)
Sex (M/F)	11/37
Zung Depression score (M/F)	
> 50	43 (8/35)
50–36	5 (3/2)
≤ 35	0
Mean (95% CI)	61.5 (58.7–64.3)
Quality of life index on VAS	
Mean (95% CI)	56.0 (51.0–61.0)
Previous opioid use	
Yes	13
No	35
% Users (95% CI)	27.1 (14.4–39.8)
Pain duration in months	
Median (range)	25 (2–254)
Baseline pain on NRS	
Mean pain intensity (95% CI)	65.2 (60.5–69.9)
Mean pain unpleasantness (95% CI)	69.8 (64.1–74.0)
Diagnostic groups	
Radiculopathy	
Acute from disc protrusion	3
Chronic from epidural fibrosis	14
Chronic idiopathic	11
Posttraumatic neuralgia	9
Postherpetic neuralgia	3
Phantom pain	2
Central pain	3
Postrhizotomy pain	3
Types of neuropathic pain	
Nociceptive nerve pain	3
Mixed neuropathic pain	25
Deafferentation pain	20
Types of sensory disturbance	
Pin-prick	
Analgesia	5
Hypalgesia	39
Hyperalgesia	17
Hyperpathia	21
Mechanical touch	
Anesthesia	10
Hypoesthesia	35
Allodynia	16
Cold disc	
Anesthesia	17
Hypoesthesia	32
Hyperesthesia	9
One or more sensory disturbance	48

M, male; F, female; VAS, visual analogue scale; CI, confidence interval; NRS, numerical rating scale.

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 $\%PID_{max}$ and $\%PID_{av}$ 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 $\%PID_{av}$ during the FENiv test and $\%PID_{av}$ 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 ($\%PID_{max}$, $\%PID_{av}$, $\%PID_{12w}$). There was no significant difference in pain relief between the group with mixed neuropathic pain and that with deafferentation pain (for example, for PID_{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

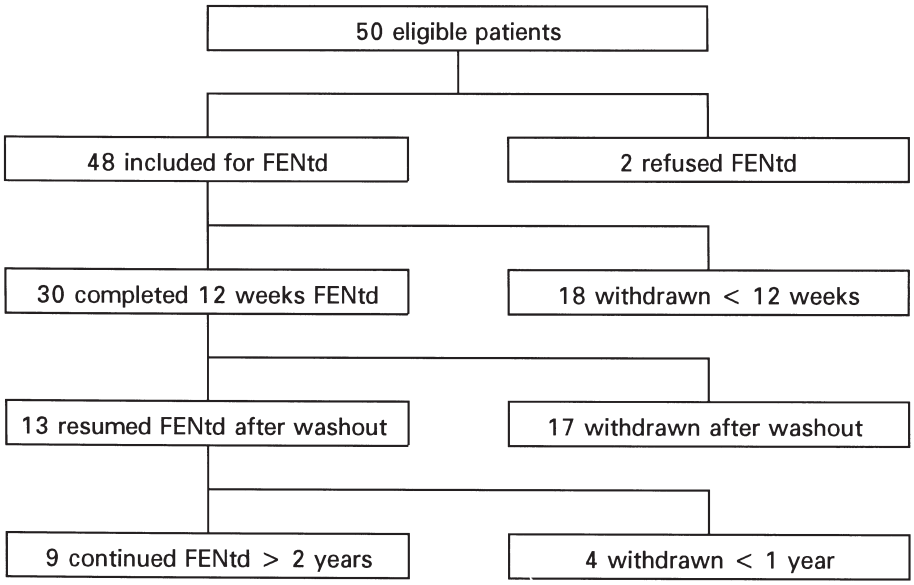

Fig. 1. Trial profile. FENtd, transdermal fentanyl.

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 FEN_{12w} patients.

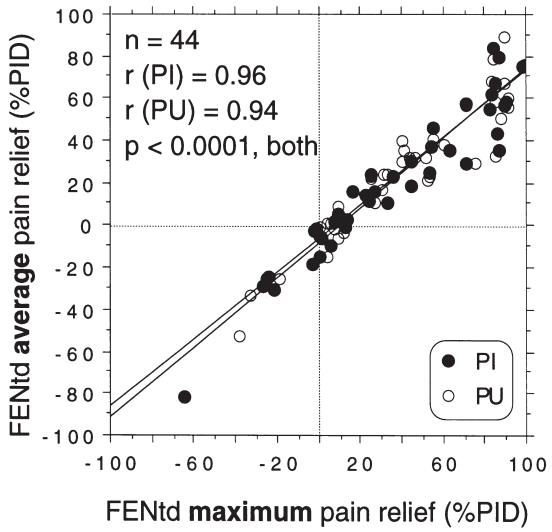

Fig. 2. Average versus maximal pain relief with FENtd. Symbols: black circles: pain intensity; open circles: pain unpleasantness ($N = 44$, $r(PI) = 0.96$, $r(PU) = 0.94$, $P < 0.0001$, both).

Quality of Life and Depression

Figure 7 illustrates that in the 30 FEN_{12w} 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

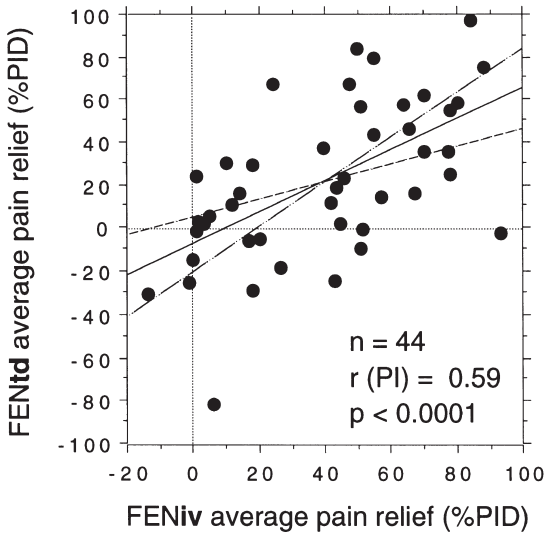

Fig. 3. Average pain relief with FENiv test versus FENtd. Symbols: see Figure 2 ($N = 44$, $r(\mathrm{PI}) = 0.59$, $P < 0.0001$)

three, and absent in four. There was no substantial change in depression scores. The severity of side effects remained low and did not preclude further FENtd therapy. In one patient 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 prolonged treatment with the opioid fentanyl suggests that substantial and sustained pain relief may be obtained in a minority of patients with noncancer neuropathic pain, including deafferentation pain. After 12 weeks of FENtd ad-

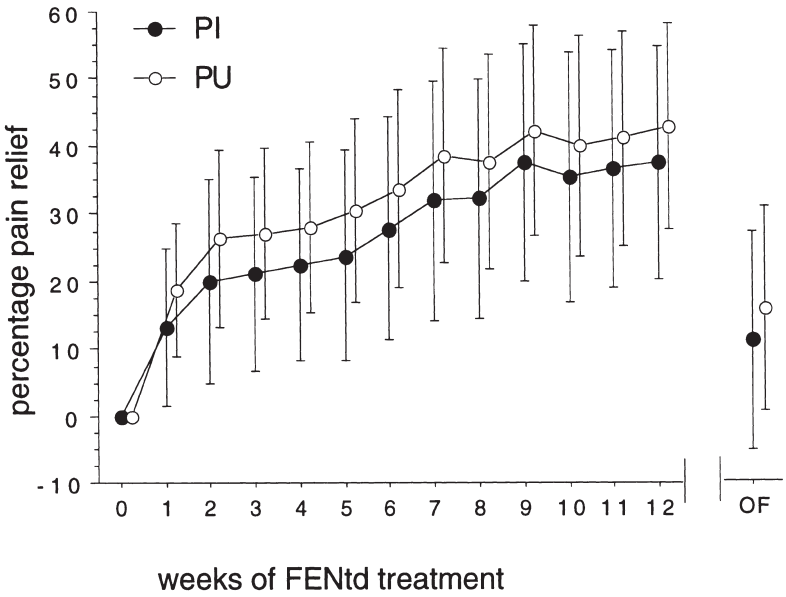

Fig. 4. Time-related pain relief with FENtd. Change in % pain-intensity (PI, black symbols) and pain-unpleasantness (PU, open symbols) compared to baseline pain in the 30 patients with neuropathic pain. Error bars: 95% confidence intervals; Negative scores indicate that pain increased. OF: opioid-free observation week.

Table 2
Pain Relief with FENtd in the Different Diagnostic Groups and Types of Neuropathic Pain

				% PID after 12 weeks FENtd		
Subgroups	pts	$\%PID_{max}$	$\%PID_{av}$	Mean	Moderate	Substantial
Radiculopathy						
Acute from disc protrusion	1	86.0	44.0	86.0	0	1
Chronic from epidural fibrosis	11	40.5	24.9	31.3	1	5
Chronic idiopathic	6	38.5	21.8	32.8	1	2
Posttraumatic neuralgia	7	49.2	36.0	35.9	2	2
Postherpetic neuralgia	1	36.1	23.4	25.0	1	0
Phantom pain	1	−1.6	−1.6	−1.6	0	0
Central pain	2	77.4	45.5	70.0	0	2
Postrhizotomy pain	1	84.2	84.2	84.2	0	1
Nociceptive nerve pain	1	86.0	44.0	86.0	0	1
Mixed neuropathic pain	17	39.8	23.8	31.8	2	7
Deafferentation pain	12	51.7	37.5	42.1	3	5
Totals	30	45.9**	29.7*	37.6*	5 (17%)	13 (43%)

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

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 3
Predictors of Substantial Pain Relief with FENtd Treatment

	% PID after 12 weeks FENtd ($\%PID_{12w}$)		
Baseline predictors	50% or more $N = 13$	less than 50% $N = 17$	*P* value
Baseline characteristics			
Age in years	52.8 (46.9–58.6)*	46.4 (38.8–54.5)	NS
Gender (M/F)	11/2	13/4	NS
Zung depression score	64.0 (59.7–68.2)	64.3 (59.2–69.3)	NS
Quality of life on VAS	51.7 (45.5–59.7)	53.4 (45.3–61.5)	NS
Previous opioid use (%)	85.6 (64.2–105.0)	64.7 (41.3–88.0)	NS
Pain duration median (range) in months	38 (1–146)	26 (2–253)	NS
Pain intensity on NRS	68.3 (59.2–77.5)	65.9 (58.4–73.5)	NS
Pain unpleasantness on NRS	70.4 (60.0–80.8)	69.9 (61.3–78.4)	NS
Type of neuropathic pain mixed versus deafferentation	7 (44%) vs. 5 (42%)	10 (59%) vs. 7 (58%)	NS
Intravenous fentanyl test			
Maximum relief of pain intensity ($\%PID_{max}$)	82.1 (69.5–95.3)	51.0 (34.2–57.8)	0.01
Average relief of pain intensity ($\%PID_{av}$)	60.2 (47.8–72.5)	29.1 (17.4–40.8)	0.001

*Between brackets: 95% confidence intervals.
M, male; F, female; VAS, visual analogue scale; CI, confidence interval; NRS, numerical rating scale.

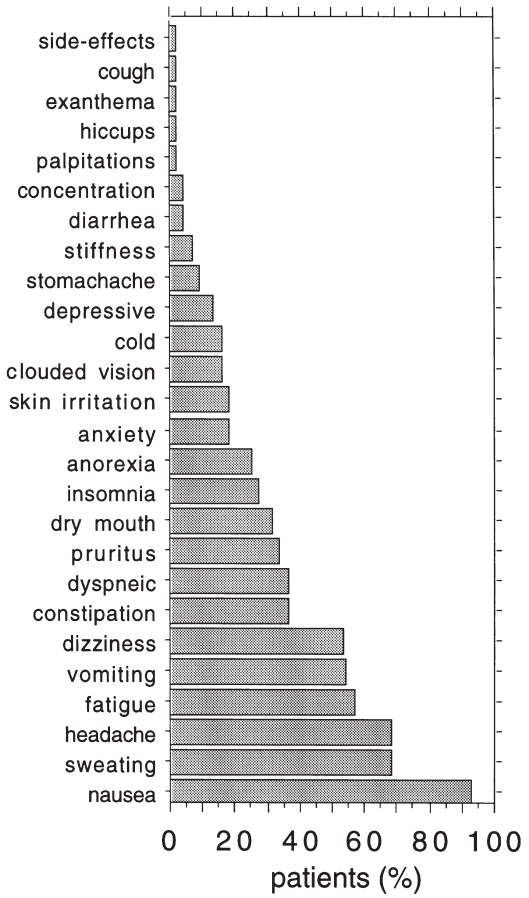

Fig. 5. Type and incidence of side effects occurring at any time of transdermal fentanyl therapy in all evaluable patients ($N = 44$).

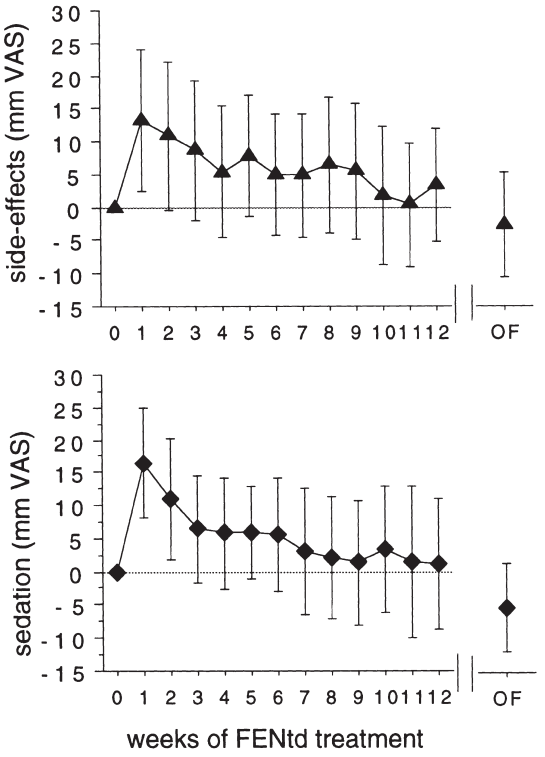

Fig. 6. Time-related severity of side effects (a) and sedation (b). Change in severity of side effects (a) and sedation (b) on a visual analogue scale (0–100 mm) during FENtd and the opioid-free (OF) observation week in the 30 patients who completed the trial (12 weeks). Error bars: 95% confidence intervals.

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,[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,[3,4,24–26] but contradicts a placebo-controlled study on the efficacy of oral morphine in chronic nonmalignant pain, in which substantial pain relief was not paralleled by functional improvement.[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 μg 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.[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

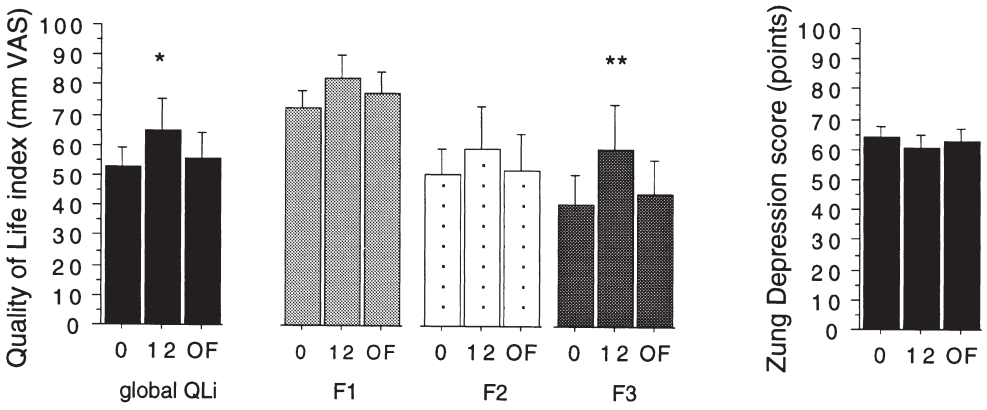

Fig. 7. Changes in quality-of-life index (QLi) and depression. Comparison of the quality-of-life index and the Zung depression score between baseline (week 0), after 12 weeks of FENtd treatment (week 12), and during the opioid-free (OF) observation week in 30 patients who completed the trial. Global QLi: sumscore of 13 items of quality of life index; Factor 1, 2, 3: subfactors of QLi, see methods. Error bars: 95% confidence intervals. Significance level $*P < 0.01$; $**P < 0.005$.

observed in patients without a history of substance abuse.[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.[4,29,30]

Although substantial pain relief with FENiv had been obtained in 58% of the same patient group,[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

We thank D. Broere, MD, B. zum Vörde sive Vörding, E. Wieldraaijer, and A. Uitdenwilligen for patient care, T.A. Hoekstra for data management, the Saint Lucas Andreas Hospital Pharmacy (A. Faber and F. Jagroep) for distribution of medication, and Janssen-Cilag, Tilburg, The Netherlands for providing fentanyl-TTS.

Table 4
Influence of Pain Relief on Depression and Quality of Life

	Pain relief after 12 weeks FENtd (%PID_{12w})		
Treatment differences	50% or more $N = 13$	Less than 50% $N = 17$	P value
Change in Zung score (points)	6.0 (−0.58 −12.4)*	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)	0.02
Factor 1: symptom control	12.3 (2.3 −22.9)	2.0 (−8.1 −12.1)	NS
Factor 2: physical well-being	14.6 (−0.59 −29.8)	−7.4 (−22.1 −7.3)	0.05
Factor 3: psychological well-being	32.4 (9.7 −55.1)	−0.5 (−14.7 −13.7)	0.02

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

References

1. Willner C and Low PA. Pharmacologic approaches to neuropathic pain. In: Dyck PJ, ed. Peripheral neuropathy. Philadelphia: Saunders, 1993: 1709–1720.

2. Portenoy RK. Neuropathic pain. In: Portenoy RK, Kanner RM, eds. Pain management: theory and practice. Philadelphia: FA Davis, 1996:83–125.

3. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage 1992;7:69–77.

4. Winkelmüller M, Winkelmüller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. J Neurosurg 1996;85:458–467.

5. Urban BJ, France RD, Steinberger EK, Scott DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. Pain 1986;24:191–196.

6. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986;25:171–186.

7. Schulzeck S, Gleim M, Maier C. Morphintabletten bei chronischen nicht-tumorbedingten Schmerzen. Welche Faktoren beeinflussen Erfolg oder Miserfolg einer Langzeittherapie? Anaesthesist 1993;42:545–556.

8. Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of non-malignant origin. J Pain Symptom Manage 1993;8:279–288.

9. Taub A. Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. In: Kitahata LM, Collins D, eds. Narcotic analgesics in anesthesiology. Baltimore: Williams and Wilkins, 1982:199–208.

10. Brena SF, Sanders SH. Opioids in nonmalignant pain: questions in search of answers. Clin J Pain 1991;7:342–345.

11. Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996; 347:143–147.

12. Portenoy RK. Chronic opioid therapy in nonmalignant pain. J Pain Symptom Manage 1990;5:46–62.

13. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence and addiction in chronic pain patients. Clin J Pain 1992;8:77–85.

14. Arnér S, Meyerson BA. Opioids in neuropathic pain. Pain Digest 1993;3:15–22.

15. Gourlay GK. Long-term use of opioids in chronic pain patients with nonterminal disease. Pain Rev 1994;1:62–76.

16. Jamison RN, Anderson KO, Peeters-Asdourian C, Ferrante FM. Survey of opioid use in chronic nonmalignant pain patients. Reg Anesth 1994;19:225–230.

17. Dellemijn PLI, Vanneste JAL. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 1997;349:753–758.

18. Bennett GJ. Neuropathic pain. In: Melzack R, Wall PD, eds. Textbook of pain. Edinburgh: Churchill Livingstone, 1994:201–224.

19. Dellemijn PLI, Fields HL, Allen RR, McKay WR, Rowbotham MC. The interpretation of pain relief and sensory changes following sympathetic blockade. Brain 1994;117:1475–1487.

20. Dellemijn PLI, Deuning C, Laman DM and van Duijn H. Sensory disturbances in neuropathic pain. In: Neuropathic pain. Thesis. University of Amsterdam. Maastricht: Shaker Publishing, 1997:45–62.

21. Kupers RC, Konings H, Adriaensen H, Gybels JM. Morphine differentially affects the sensory and affective pain ratings in neurogenic and idiopathic forms of pain. Pain 1991;47:5–12.

22. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63–70.

23. Padilla GV, Presant C, Grant MM, Metter G, Lipsett J, Heide F. Quality of life index for patients with cancer. Res Nurs Health 1983;6:117–126.

24. Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic non-malignant pain treated with long-term oral narcotic analgesics. Ann Clin Psychiatry 1992;4:185–192.

25. Finlayson RD, Maruta T, Morse BR, Martin BA. Substance dependence and chronic pain: experience with treatment and follow-up results [Abstract]. Pain 1986;26:175–180.

26. France RD, Urban BJ, Keefe FJ. Long-term use of narcotic analgesics in chronic pain. Soc Sci Med 1984;19:1379–1382.

27. Ahmedzai S, Brooks D, on behalf of the TTS-fentanyl Comparative Trial Group. Transdermal fentanyl versus sustained-release morphine in cancer pain: preference, efficacy, and quality of life. J Pain Symptom Manage 1997;13:254–261.

28. Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980;302:123.

29. Medina JI, Diamond S. Drug dependency in patients with chronic headache. Headache 1977;17: 12–14.

30. Perry S, Heidrich G. Management of pain during debridement: survey of US burn units. Pain 1982;13:267–280.