Effectiveness and Tolerability of the Buprenorphine Transdermal System in Patients with Moderate to Severe Chronic Pain: A Multicenter, Open-Label, Uncontrolled, Prospective, Observational Clinical Study

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ABSTRACT

Background: A new transdermal delivery system (TDS) for the rate-controlled systemic delivery of buprenorphine is available in 3 patch strengths, with release rates of 35, 52.5, and 70 μg/h over 72 hours, delivering daily amounts of 0.8, 1.2, and 1.6 mg, respectively. Randomized, double-blind, placebo-controlled, Phase III clinical trials in >400 patients with severe pain of malignant or nonmalignant origin have shown the analgesic efficacy of buprenorphine TDS.

Objective: This study investigated the effectiveness and tolerability of buprenorphine TDS for the relief of chronic pain in routine clinical practice.

Methods: This was a multicenter, open-label, uncontrolled, prospective, observational, 3-month follow-up study in patients who were beginning buprenorphine TDS treatment for moderate to severe cancer or noncancer pain that had not responded to nonopioid analgesics. Patches were to be changed every 72 hours. Patients were evaluated at 1 and 3 months after the start of treatment. Those who dropped out were considered treatment failures. Pain relief was assessed on a 5-category verbal rating scale, and quality of life was assessed using the European Quality of Life 5D (EQ-5D) questionnaire. Tolerability was determined based on adverse events recorded during the follow-up period.

Results: The study recruited 1223 patients, most of whom were outpatients. Of the 1212 patients for whom sex data were available, 820 (67.7%) were women. In the 1188 patients with age data, the mean (SD) age was 64.9 (12.9) years. In the 1175 patients with data on the etiology of pain, 82.4% had noncancer pain. Six hundred eighty-eight (56.3%) patients completed the 3-month follow-up period. The median daily amount of buprenorphine TDS received at the beginning of the study was 0.8 mg (corresponding to 35 μg/h). Over the study period, there was a significant increase in the proportion of patients reporting very good or good pain relief ($P < 0.001$), from 3.6% (43/1205) at baseline to 63.2% (762/1205) after 1 month and 56.8% (685/1205) after 3 months. Quality of life also improved, from a mean (SD) EQ-5D score of 40.6 (20.5) at baseline to 56.8 (23.5) at 3 months ($P < 0.001$). Five hundred seventeen (42.3%) of the original 1223 patients experienced adverse events; the investigator judged 397 (32.5%) of these events possibly or probably related to study drug. The likelihood of experiencing a drug-related adverse event was greater in noncancer patients than in cancer patients. The most common adverse events were nausea (11.0%), vomiting (9.2%), and constipation (7.8%); the most common local adverse events were pruritus (1.4%), dermatitis (1.3%), and erythema (1.3%).

Conclusion: In the population studied, buprenorphine TDS was effective in alleviating cancer and noncancer pain and was well tolerated overall. (*Clin Ther.* 2005;27:451–462) Copyright © 2005 Excerpta Medica, Inc.

Key words: buprenorphine, observational study, cancer pain, noncancer pain, transdermal system, opioids.

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INTRODUCTION

There have been substantial advances in the effective pharmacologic management of chronic pain in recent years. Nonetheless, basic and clinical research continues to look for new clinically effective drug treatments and better ways of delivering them (eg, controlled-release oral formulations, transdermal delivery systems [TDS]).

Transdermal drug delivery, which relies primarily on the use of occlusive patches, is an established technology. This method facilitates the administration of drugs that have limited bioavailability after oral intake. In addition, because this method works like a sustained-release formulation, it avoids the peaks and troughs in drug concentration seen with oral formulations, thus reducing the risk of adverse events. It also may improve compliance by avoiding the need for frequent dosing.[1] World Health Organization guidelines for the treatment of chronic cancer pain state, among other principles, that analgesics used to treat chronic pain should not induce sudden peaks in serum concentrations, which are often responsible for adverse events.[2] Thus, TDS offer a solution to the problem of administering analgesics to patients with chronic pain.[3]

Despite the advantages, there are some limitations to the use of TDS. The long interval between reapplication of patches relative to other dosing forms, which increases convenience during periods of stable dosing, may be a disadvantage when the amount of drug has to be adjusted (eg, at the start of therapy). Because a gradient of drug has to develop across the skin for the system to work, there is a delay in the onset/decline of effect that may cause problems, particularly in obese patients or when drug delivery has to be stopped suddenly. Also, dosing may be affected by both intrasubject and intersubject variability in factors such as skin hydration and/or temperature at various anatomic sites, skin type, and age. Finally, the adhesive on the patch may irritate some patients' skin.[4] Postmarketing research is useful in determining the importance of these disadvantages in clinical practice.

Opioids play an important role in the management of pain of several origins. They are effective in alleviating cancer-related pain, particularly moderate to severe pain,[2,5] and are being used increasingly in the long-term management of chronic pain of noncancer origin.[6] Buprenorphine is a semisynthetic opiate derived from the alkaloid thebaine (oripavine), which exhibits partial agonist activity at the μ-opioid receptor[7,8] and antagonist activity at the κ-opiate receptor.[9] Its main pharmacologic properties are high analgesic potency (25–40 times greater than that of morphine), prolonged duration of action, limited respiratory depressant activity, and a less rapid and intense withdrawal syndrome compared with pure μ-receptor agonists such as morphine.[10–12] Several studies comparing the characteristics of buprenorphine and other opioids in various chronic pain conditions reported that buprenorphine was potent and efficacious, particularly in the treatment of dull pain, and had less potential to cause withdrawal symptoms, despite a longer duration of adverse effects compared with morphine.[13–15]

Buprenorphine's high analgesic potency, high lipophilicity, and low molecular weight make it ideal for delivery in a transdermal formulation. Advanced patch technology has produced a new TDS for the rate-controlled systemic delivery of buprenorphine. Buprenorphine TDS is available in 3 patch strengths, with release rates of 35, 52.5, and 70 μg/h over 72 hours, delivering daily amounts of 0.8, 1.2, and 1.6 mg, respectively.[16]

Three randomized, double-blind, placebo-controlled, Phase III clinical trials in >400 patients with severe pain of malignant or nonmalignant origin have shown the analgesic efficacy of buprenorphine TDS.[17–19] These studies reported consistently greater proportions of responders ($P = 0.032$ for 35 μg/h; $P = 0.003$ for 52.5 μg/h[18]), lower pain intensity scores (P = NS, possibly because the studies focused on qualitative end points), and less use of rescue medication ($P = 0.010$[18] and $P = 0.001$[19]) among patients who received buprenorphine TDS compared with those who received placebo. Importantly, buprenorphine TDS had clinical efficacy in patients who had not received adequate pain relief with weak opioids or morphine. The incidence of systemic adverse events was highly variable (from 23% in the shortest study[17] to 69% in the longest[18]), possibly due to differences in the study designs (eg, duration, presence of a run-in period, previous exposure to opioids). Most systemic adverse events were of mild to moderate intensity and were consistent with the known effects of opioid treatment. Local adverse events affected ~25% of patients and were generally mild to moderate and transient.

To the authors' knowledge, 2 systematic observational studies of the effectiveness and safety of buprenorphine TDS in large numbers of patients have

been reported at scientific meetings.[20,21] Observational studies have several advantages over randomized controlled trials, including lower cost, longer observation periods, and a wider range of patients.[22] They usually provide valid information about the use of a drug in clinical practice, as well as identifying rare adverse events and risk factors not seen in randomized clinical trials. This article reports the findings of a 3-month observational study of the outcomes of buprenorphine TDS treatment in a large group of patients with moderate to severe chronic cancer or noncancer pain in routine clinical practice. This information should be useful to clinicians, as it complements data from the premarketing randomized trials.

PATIENTS AND METHODS

Patient Population

The study included men and women aged ≥18 years who had the physical and mental capacity to participate in the study and were receiving outpatient or inpatient treatment for moderate to severe cancer pain or noncancer pain that had not responded to nonopioid analgesics, and for whom buprenorphine TDS was indicated as analgesia. According to the Spanish prescribing information,[23] use of buprenorphine TDS is contraindicated in pregnant or breastfeeding women, patients with a known hypersensitivity to buprenorphine, those with an addiction to opioids or receiving treatment for narcotics withdrawal symptoms at the time of enrollment, patients with a diagnosis of severe myasthenia or delirium tremens, those with altered respiratory function or serious alteration of the respiratory center, and those receiving monoamine oxidase inhibitors at the time of inclusion or during the previous 2 weeks. Such patients were excluded from the study.

Study Design

This was a multicenter, open-label, uncontrolled, prospective, observational, 3-month follow-up study involving the participation of physicians in the following units or specialties: rheumatology, rehabilitation, traumatology, oncology, palliative care, and pain. Physicians from all regions of Spain were invited to become study investigators so the sample would be as representative as possible. Those who accepted were paid on the basis of patients recruited and observed. Patients received care and treatment through the Spanish Public Health Service; they received no payment for their participation and were unaware of payments made to the participating physicians.

Patients began buprenorphine TDS therapy at the lowest possible amount (based on the physician's judgment and the available patch strengths). Thereafter, the amount could be modified at the physician's discretion based on the adequacy of analgesia and patients' clinical status. Patches were replaced every 72 hours, as recommended in the product information. Amounts of buprenorphine TDS used were recorded throughout the study. Investigators could prescribe concomitant medications for pain, including sublingual buprenorphine, to adjust analgesia during a transition between patch strengths.

The study complied with statutory requirements for conducting postauthorization observational studies in Spain and was approved by 14 accredited regional ethics committees. All patients gave their written informed consent.

Efficacy and Tolerability Assessments

Data collection was based on prescriptions written in clinical practice. As the use of buprenorphine TDS is indicated for the treatment of moderate to severe pain that has not responded to nonopioid analgesics, it was assumed that this criterion had been met and no assessment of baseline pain severity was made. In no case was patients' treatment modified because of their inclusion in the study. The initial evaluation included demographic data (age and sex), clinical data (systolic and diastolic blood pressure, body weight, height, and heart rate), causes of pain, and use of concomitant analgesic and/or nonanalgesic medication. Pain relief was evaluated before application of the first patch using a verbal rating scale (*very good, good, medium, bad*, and *no effect*).[24] Quality of life (QoL) was measured using the European Quality of Life 5D (EQ-5D) questionnaire.[25] Additional evaluations were conducted after 1 and 3 months of treatment. Attempts were made to contact patients who failed to attend scheduled study visits or at least obtain information on their reasons for withdrawal. When these efforts failed, patients were considered lost to follow-up.

In addition to the pain relief and QoL ratings, information was collected at months 1 and 3 on changes in vital signs, use of concomitant analgesic medication, and treatment compliance (investigator's subjective evaluation). Information on changes in sleep quality and ease of handling the patches was

recorded using verbal rating scales. Sleep quality was rated as *significant improvement, improvement, no change, slight worsening*, or *worsening*. Ease of handling was rated as *absolutely no problems, easy, somewhat complicated*, or *difficult*.[24]

Adverse events occurring during the follow-up period were recorded and coded using the Medical Dictionary for Regulatory Activities* (MedDRA version 6.1).[26] Specific information related to each event (beginning date, intensity, seriousness, outcome, treatment, and investigator's evaluation of the relationship to study medication) was also recorded.

The primary effectiveness and tolerability measures were the proportion of patients reporting very good or good pain control and the proportion of patients experiencing ≥1 treatment-related adverse event. Secondary measures of effectiveness were changes in QoL and sleep quality during the follow-up period.

Statistical Analysis

In the descriptive analysis, absolute frequency and 95% CIs were used for qualitative variables, and central trend and dispersion measurements were used for quantitative variables. Analysis of variance or chi-square tests (Student or Fisher) were used to study associations, and the Student *t* test for paired data or the McNemar test[27] was used for longitudinal analysis of the data, with the ji2 trend test[27] and analysis of covariance used to adjust for baseline. Given the large size of the sample, it was assumed that the descriptors followed a normal distribution.

Two data sets were analyzed. The observed-case set included all patients who completed follow-up and had available postbaseline data. The worst-case set included all patients for whom at least the baseline value for a given parameter was available; missing postbaseline data were imputed by carrying forward the last available observation (or the baseline value if there was no last available observation; that is, if all dropouts failed).

Adjusted analyses of effectiveness (pain relief and QoL) and tolerability after 3 months of treatment were performed using regression analysis. In the logistic regression analysis of pain relief, the dependent variable was the presence of pain relief, and the explanatory variables were increase in the amount of drug administered during the follow-up period, satisfactory pain relief at baseline, use of concomitant analgesic medication, cause of pain (cancer vs noncancer), age, and sex. For QoL, a multiple linear regression model was constructed in which the dependent variable was the EQ-5D score and the explanatory variables were achievement of pain relief, increase in the amount of buprenorphine TDS during the follow-up period, use of concomitant analgesic medication, cause of pain (cancer vs noncancer), age, and sex. Another logistic regression model was constructed for the analysis of tolerability; the dependent variable was the existence of ≥1 treatment-related adverse event, and the explanatory variables were the initial amount of buprenorphine TDS (defined in terms of 2 derived variables [<35 μg/h vs 35 μg/h and <35 μg/h vs >35 μg/h] to compare the reference cohort [those who started at <35 μg/h] with both those who started at 35 μg/h and those who started at higher patch strengths), body mass index (BMI) ≥27 kg/m^2, cause of pain (cancer vs noncancer), and use of concomitant analgesic medication.

Possible interactions between variables were also evaluated in the models. The explanatory variables *increase in the amount of buprenorphine* and *achievement of pain relief* were imputed by assuming that an increase occurred and that pain relief was not achieved whenever postbaseline data were not available to construct the worst-case set.

RESULTS

Between December 2002 and April 2004, 1223 patients were recruited by 241 physicians at 56 centers. Nearly all were outpatients. Sex data were available for 1212 patients, of whom 820 (67.7%) were women. For the 1188 patients with available data, the mean (SD) age was 64.9 (12.9) years. Recruitment took place mainly at rheumatology services (439/1223 patients [35.9%]) and pain units (269/1223 patients [22.0%]). Data on the cause of pain were available for 1175 patients, of whom 968 (82.4%) had noncancer pain. The locomotor system was most frequently implicated (87.5%) in noncancer pain, followed by surgical sequela (7.1%) and pain of neuropsychiatric origin (5.1%). Blood pressure ≥140/90 mm Hg was recorded in 661 of 1140 patients (58.0%), and 291 of 1133 patients (25.7%) were obese (**Table I**).

*Trademark: MedDRA® (International Federation of Pharmaceutical Manufacturers Association, Geneva, Switzerland).

Table I. Baseline characteristics of study patients (N = 1212).

Variables	
Sex, no. (%)	
Female	820 (67.7)
Male	392 (32.3)
Age, y (n = 1188)	
Mean (SD)	64.9 (12.9)
Heart rate, beats/min (n = 1124)	
Mean (SD)	78.3 (11.4)
Body weight, kg (n = 1154)	
Mean (SD)	72.5 (13.6)
Blood pressure ≥140/90 mm Hg, n/N (%)	661/1140 (58.0)
BMI >30 kg/m^2, n/N (%)	291/1133 (25.7)
Cause of pain, n/N (%)	
Cancer	207/1175 (17.6)
Noncancer	968/1175 (82.4)
Locomotor/musculoskeletal	847/968 (87.5)
Surgical sequela	69/968 (7.1)
Neuropsychiatric	49/968 (5.1)
Gastrointestinal	45/968 (4.6)
Cardiovascular	32/968 (3.3)
Genitourinary	24/968 (2.5)
Endocrine/metabolic	20/968 (2.1)
Other	59/968 (6.1)

BMI = body mass index.

Of the patients initially recruited, 688 (56.3%) completed the 3-month follow-up period. The reasons for premature withdrawal were adverse events (252 patients [20.6%]), loss to follow-up (111 [9.1%]), and lack of effectiveness (61 [5.0%]). No reason was specified by 70 patients (5.7%). Forty-one (3.4%) patients discontinued treatment before the third month because of pain improvement.

Of the 688 patients who completed the study, 633 (92.0%) stated that they had complied with 80% of prescribed treatment. The median daily amount of buprenorphine TDS at the beginning of the study was 0.8 mg (corresponding to 35 µg/h). The proportion of patients receiving patch strengths delivering ≥52.5 µg/h increased significantly over the course of the study, from 2.3% at baseline to 10.4% at month 1 and 19.8% at month 3 ($P < 0.001$).

Table II shows the absolute and relative frequencies of changes in patch strengths at months 1 and 3. At the end of the observation period, 76.1% of patients had no change, and 22.3% had been changed to a higher patch strength. Weak opioids were used as concomitant analgesic medication in 22.6% of patients, with tramadol being the most frequently prescribed (19.7%). Consistent with known opioid effects, the main concomitant nonanalgesic medications were antiemetics (19.0%) and laxatives (11.1%).

Regarding changes in sleep quality, 63.2% (668/1057) of patients reported an improvement in this parameter after 1 month of treatment, with an increase to 70.8% (596/842) in the observed-case set and a decrease to 56.4% (596/1057) in the worst-case set after 3 months (Table III).

Of the 1106 patients who answered the question regarding the ease of handling of buprenorphine TDS, 41 (3.7%) considered its handling somewhat complicated and 9 (0.8%) found it difficult to use. Patients changed the patch themselves in 671 of 1026 (65.4%) recorded instances.

Table II. Absolute and relative frequency (no. [%]) of patients with ≥1 change in strength of buprenorphine transdermal delivery system from baseline to months 1 and 3.

Change in Patch Strength	Month 1 (n = 989)	Month 3 (n = 606)
Changed to a higher strength	120 (12.1)	135 (22.3)
Not changed	844 (85.3)	461 (76.1)
Changed to a lower strength	25 (2.5)	10 (1.7)

Table III. Absolute and relative frequency (no. [%]) of responses on the verbal rating scale for sleep quality, change from month 1 to month 3 in the worst-case analytic set* (n = 1057).

Response	Month 1 (n = 1057)	Month 3 (n = 1057)
Significant improvement	148 (14.0)	184 (17.4)
Improvement	520 (49.2)	412 (39.0)
No change	319 (30.2)	213 (20.2)
Slight worsening	51 (4.8)	26 (2.5)
Worsening	19 (1.8)	7 (0.7)

*Patients for whom at least the baseline value was available.

Pain Relief

Data on pain relief were available for 1205 patients at baseline, for 1080 patients at month 1, and for 827 patients at month 3. Of the 1205 patients with baseline data, 43 (3.6%) reported that they had very good or good pain relief before starting buprenorphine TDS (because this was an observational study, the criterion for recruitment was a prescription for buprenorphine TDS, not pain relief scores at entry). In the worst-case set, there was a significant increase in the proportion of patients with very good or good pain relief at months 1 and 3 (both, $P < 0.001$), from 3.6% (43/1205) at baseline to 63.2% (762/1205) after 1 month and 56.8% (685/1205) after 3 months (**Figure 1**). The corresponding proportions in the observed-case set were higher (these can be calculated by dividing the absolute frequencies by 1080 and 827, the numbers of patients completing the month-1 and final evaluations, respectively).

When pain relief was stratified by the cause of pain (cancer or noncancer), the proportion of patients reporting very good or good pain relief differed nonsignificantly after 1 month (65.3% and 62.1%, respectively). After 3 months, there was not even an important numerical difference in pain relief between the groups with cancer or noncancer pain (56.8% and 57.3%).

When pain relief was stratified by concomitant analgesic medication (use or nonuse), the proportion of patients reporting satisfactory pain relief was nonsignificantly higher in those who used concomitant analgesics compared with those who did not (58.2% and 54.6%, respectively).

There was a clear relationship between pain relief and the amount of buprenorphine administered, as patients who required a higher patch strength were those who had inadequate pain relief ($P < 0.001$). The amounts of buprenorphine TDS used were higher in cancer patients than in noncancer patients, with 43.3% of cancer patients and 14.0% of noncancer patients requiring patch strengths ≥52.5 μg/h at month 3 ($P < 0.001$).

Adjusted Analyses

In model 1, there was a lower probability of pain relief in patients who were switched to a higher patch

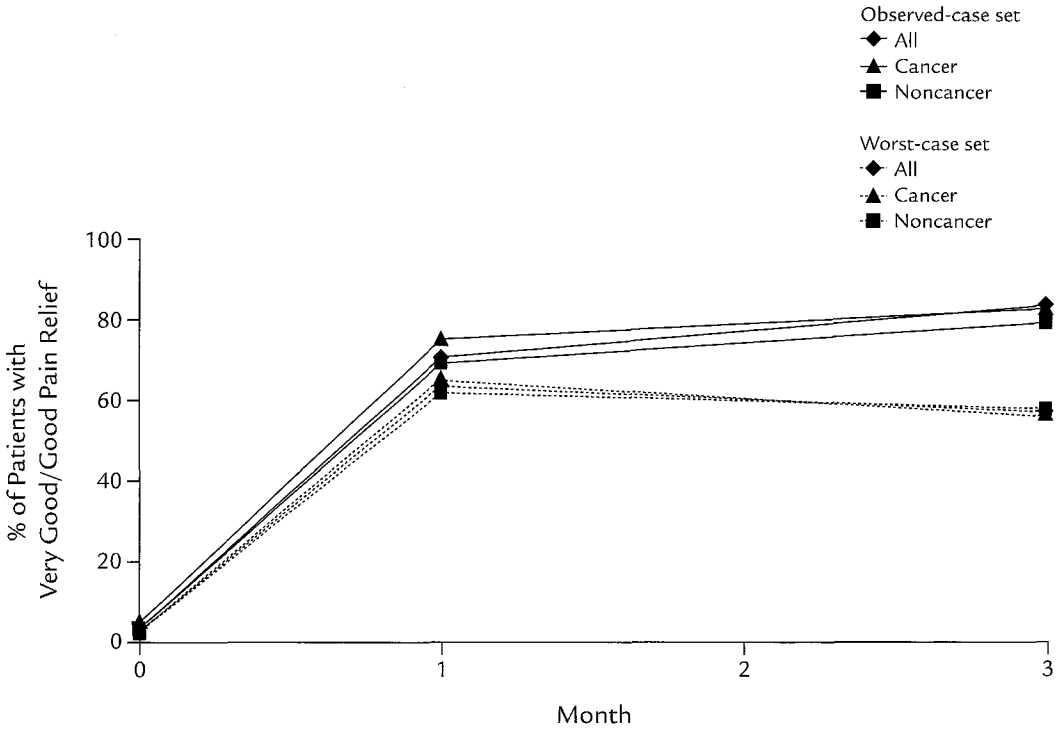

Figure 1. Proportions of patients experiencing very good or good pain relief in the total population and by cause of pain in the observed-case set (all patients who completed follow-up and had available postbaseline data; n = 827) and the worst-case set (patients for whom at least the baseline value was available; n = 1205).

strength during the follow-up period (adjusted odds ratio [OR], 0.11; 95% CI, 0.08–0.14) and a greater probability of pain relief in cancer patients compared with noncancer patients (adjusted OR, 1.39; 95% CI, 0.94–2.04), regardless of the amount of buprenorphine TDS, use of concomitant analgesic medications, age, or sex (**Table IV**). The probability of achieving pain relief was more than 10-fold greater in patients reporting very good or good pain relief at baseline compared with those who did not, but this result is of little significance, as patients with good pain relief at baseline (n = 43) would be more likely to have good pain relief at the end of the study.

Quality of Life

In the evaluation of QoL, the worst-case set had a mean (SD) increase of 16.1 (26.7) points on the EQ-5D questionnaire score (median increase, 10 points; range, –87 to 90 points), from 40.6 (20.8) points at baseline (median, 40 points; range, 0 to 100 points) to 56.8 (23.5) points after 3 months of treatment (median, 60 points; range, 0 to 100 points) ($P < 0.001$). In the observed-case set, there was a mean increase of 24.1 (28.3) points (median, 29 points; range, –87 to 90 points), from 40.2 (19.5) points at baseline (median, 40 points; range, 0 to 100 points) to 64.4 (19.9) points after 3 months (median, 70 points; 0 to 100 points) ($P < 0.001$). After 3 months, there were increases in the proportions of patients in the worst-case set who reported having no problems on the EQ-5D domains for mobility (from 20.3% at baseline to 35.1% at month 3), self-care (from 28.5% to 50.7%), and usual activities (from 11.3% to 28.7%), and a decrease in the proportion of patients who reported a lot of pain/discomfort (from 73.0% to 25.9%) or a lot of anxiety/depression (from 23.7% to 11.5%) (all, $P < 0.001$) (**Figure 2**).

No association was observed between QoL and the cause of pain, use of concomitant analgesic medica-

Table IV. Adjusted analyses of pain relief (model 1), quality of life (model 2), and adverse events (model 3) after 3 months of treatment with buprenorphine transdermal delivery system (TDS).

Variable	Statistic
Model 1	Adjusted OR (95% CI)
Increase/no increase in amount of buprenorphine TDS during follow-up	0.11 (0.08 to 0.14)
Very good–good/medium–bad–no pain relief at baseline	11.74 (3.75 to 32.67)
Age (treated as an ordinal)	1.00 (0.99 to 1.01)
Male/female sex	1.18 (0.85 to 1.62)
Cancer/noncancer pain	1.39 (0.94 to 2.04)
Use/nonuse of concomitant analgesics during follow-up	1.17 (0.86 to 1.59)
Model 2	Point Estimate
Very good–good/medium–bad–no pain relief during follow-up	20.88 (17.95 to 23.80)
Increase/no increase in amount of buprenorphine TDS during follow-up	–2.36 (–5.24 to 0.53)
EQ-5D score at baseline	0.35 (0.29 to 0.41)
Male/female sex	0.11 (–2.63 to 2.86)
Age (treated as an ordinal)	–0.02 (–0.12 to 0.07)
Cancer/noncancer pain	0.00 (–3.37 to 3.37)
Use/nonuse of concomitant analgesics during follow-up	–0.75 (–3.39 to 1.89)
Model 3	Adjusted OR (95% CI)
Patch strength	
<35 μg/h/35 μg/h	1.01 (0.54 to 1.88)
<35 μg/h/>35 μg/h	2.15 (0.76 to 6.08)
BMI ≥27 kg/m^2/BMI <27 kg/m^2	1.02 (1.00 to 1.05)
Cancer/noncancer pain	0.31 (0.19 to 0.47)
Use/nonuse of concomitant analgesics during follow-up	1.56 (0.94 to 2.58)

OR = odds ratio; EQ-5D = European Quality of Life 5D questionnaire; BMI = body mass index.

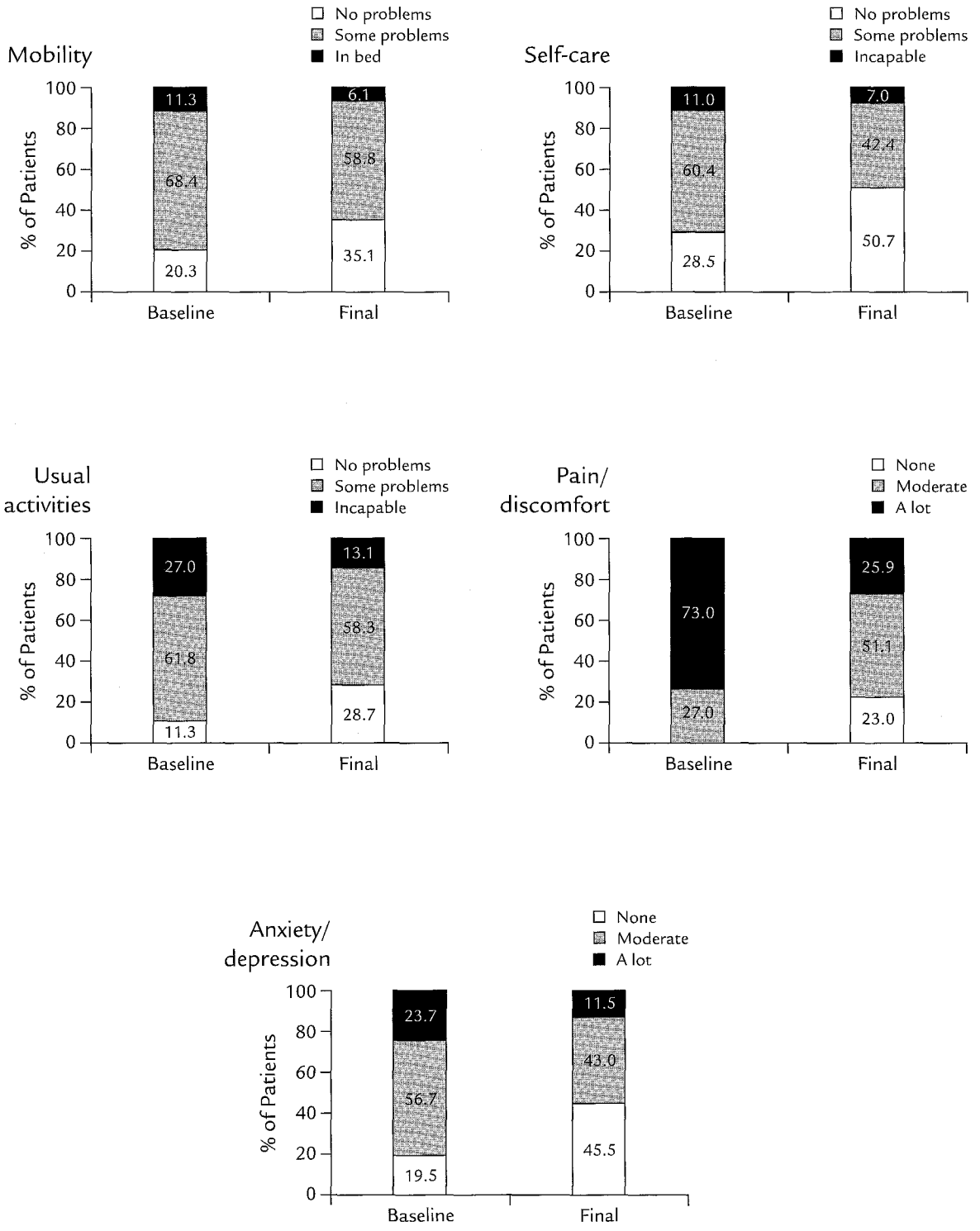

Figure 2. Change in responses on the domains of the European Quality of Life 5D questionnaire in the worst-case set (patients for whom at least the baseline value was available; n = 1216 for mobility and self-care, n = 1217 for usual activities, n = 1211 for pain/discomfort, and n = 1218 for anxiety/depression). Percentages may not total 100 due to rounding.

tion, amount of buprenorphine TDS, or sex. However, patients who reported very good or good pain relief had a significant increase in EQ-5D score (mean [SD] increase, 65.2 [20.4]; median, 70; range, 0–100) compared with those who did not report pain relief (mean increase, 49.6 [21.0]; median, 50; range, 4–100) ($P < 0.001$).

Adjusted Analyses

In model 2, there was a 20.88-point increase in EQ-5D score (95% CI, 17.95–23.80) in patients reporting very good or good pain relief compared with those who reported any other category of pain relief, independent of the amount of buprenorphine TDS, cause of pain, concomitant analgesic medication, age, or sex (**Table IV**). Patients with the highest EQ-5D score at baseline had the smallest improvements at month 3 (parameter estimate, 0.35; 95% CI, 0.29–0.41).

Tolerability

Five hundred seventeen of 1223 (42.3%) patients who began treatment with buprenorphine TDS had ≥1 adverse event during the follow-up period (95% CI, 39.5–45.1). The investigator could not dismiss the possibility of an association with study drug for 397 (32.5%) of these events (95% CI, 29.8–35.2). Withdrawals due to an adverse event possibly associated with study drug occurred in 170 (13.9%) patients (95% CI, 12.0–15.9); in 2 (0.2%) cases, the event leading to withdrawal (general discomfort and incapacity to perform daily activities) was judged serious (95% CI, 0.02–0.59).

Fifty-seven patients died during the study from causes not associated with buprenorphine TDS. Thirty cancer patients died due to progression or complication of neoplasm; 17 noncancer patients died from various causes (3 from respiratory failure; 2 each from renal failure, hepatic failure, intestinal occlusion, and pulmonary embolism; 1 each from hemoptysis, obstructive jaundice, coma, hepatic encephalopathy, pancytopenia, and cerebrovascular accident); and 10 noncancer patients died of unspecified causes.

The most frequent adverse events were nausea (11.0%), vomiting (9.2%), constipation (7.8%), dizziness (7.5%), drowsiness (4.0%), retching (3.7%), generalized pruritus (2.0%), and headache (1.6%). Local adverse events affected 6.2% of patients; the most frequent of these events were local pruritus (1.4%), dermatitis (1.3%), and erythema (1.3%). No association was observed between these events and increases in the amount of buprenorphine TDS over the follow-up period. Other adverse events were reported in <1% of patients. There were no changes in blood pressure or heart rate over the course of the study.

No association was observed at 3 months between the occurrence of ≥1 adverse event and the patch strength administered at the onset of treatment; 14 of 28 (50.0%) patients starting at a patch strength >35 μg/h experienced an adverse event, compared with 495 of 1181 (42.0%) patients starting at a patch strength ≤35 μg/h. Similarly, there was no association at 3 months between the occurrence of an adverse event and a BMI ≥27 kg/m^2; 42.2% of patients with a BMI ≥27 kg/m^2 experienced an adverse event, compared with 42.4% of those with a BMI <27 kg/m^2. A numerically greater proportion of patients who used concomitant analgesic medication experienced an adverse event compared with those who did not use concomitant analgesic medication (43.1% vs 35.7%, respectively), but the difference did not reach statistical significance. Similarly, a numerically greater but nonsignificant proportion of patients with noncancer pain experienced an adverse event compared with those with cancer pain (43.7% vs 36.7%, respectively).

Adjusted Analyses

In model 3, no significant association was observed between the occurrence of ≥1 treatment-related adverse event and any of the independent variables: initial buprenorphine TDS patch strength, BMI ≥27 kg/m^2, cause of pain, or use of concomitant analgesic medications. A significant association was observed between the occurrence of ≥1 adverse event and the cause of pain: the likelihood of an adverse event was significantly greater in patients with a nonmalignant condition (OR, 0.31; 95% CI, 0.19–0.47), in whom the incidence was approximately double that in patients with a malignant condition (**Table IV**). This also was observed when adverse events considered definitely unrelated to study drug were included in the model (data not shown).

DISCUSSION

Buprenorphine has been studied and used for >25 years in the management of pain. A transdermal formulation was approved in many European countries in 2001, and experience with this formulation is now accumulating in clinical practice. Previous placebo-

controlled studies have shown buprenorphine TDS to be clinically effective and well tolerated in patients with pain of malignant or nonmalignant origin.[17–19,28] The present study provides information on the effectiveness and tolerability of 3 months of therapy with buprenorphine TDS for pain of various origins in 1223 patients from actual clinical practice, nearly all of them outpatients.

This prospective study supports the pain-relief findings of previous controlled clinical trials of buprenorphine TDS[17–19] and provides additional information on pain relief with chronic treatment. The proportion of patients who experienced pain relief increased throughout the follow-up period, even when dropouts were considered as failures. Despite the intention to collect data on patients' concomitant medications, this information was not recorded systematically and the few data available did not allow reliable estimation on the influence of these medications on the outcome. Nevertheless, buprenorphine TDS was the main therapy used throughout the observation period and can be considered the main contributor to the results.

Sleep quality is a good index of the quality of analgesia in patients with chronic pain. This study confirmed the results of Böhme and Likar[17] and Sittl et al,[18] who reported that patients who received buprenorphine TDS had a higher proportion of nights with good sleep (>6 hours).

Buprenorphine TDS treatment was well tolerated, with adverse events occurring in less than one third of patients. The incidence of adverse events was approximately 2-fold greater among those with pain of nonmalignant origin compared with those whose pain was of malignant origin. A similar finding was reported in a review of 3 randomized, placebo-controlled, Phase III trials evaluating the efficacy and tolerability of buprenorphine TDS.[29] This observation may be explained by the difficulty of identifying the cause of an adverse event in patients with cancer pain, as investigators tend to attribute events to the underlying cancer, and most of these patients are receiving concomitant medications, are in poor clinical condition, and have a preexisting florid profile of untoward events. This explanation is supported by the findings of the present study, as differences in the incidence of adverse events between both groups (patients with cancer and noncancer pain) decreased when all adverse events were considered.

Patients found that it was easy to handle the patch; fewer than one third required assistance from family members. In a preliminary analysis of a long-term follow-up study, Radbruch and Vielvoye-Kerkmeer[30] reported that almost 95% of patients found the patch user-friendly, contributing to good compliance and improved QoL. This finding is important in clinical practice, where it is desirable that patients maintain their independence as long as possible.

The incidence of local adverse events in this study was lower than that reported in randomized trials.[29] This may be attributed to the less rigorous design of observational studies, in which there are multiple dropouts. Nevertheless, this finding is interesting, as skin irritation did not seem to be an important disadvantage over 3 months of use.

Obesity (BMI ≥27 kg/m^2) was not associated with an increase in the incidence of adverse events, which suggests that obese patients did not have particular difficulty using the patches. There were no problems associated with the delayed onset/wearing off of effect or dosing variability inherent in transdermal delivery. Treatment with buprenorphine TDS allowed the flexibility of concomitant use of other opioids as rescue medication (eg, sublingual buprenorphine, oral tramadol) before or during the transition to another patch strength without being associated with specific adverse events.

Study Limitations

Although randomized controlled trials are at the top of the hierarchy of evidence, observational studies provide effectiveness data obtained under routine clinical practice conditions (eg, subject to such confounding factors as noncompliance, polypharmacy, disease severity, and lifestyle), include a broader range of patients, and can cover longer time spans. However, observational studies have inherent sources of bias: the absence of randomization tends to result in an overestimation of effect,[31] and the presence of unrecognized factors may seriously distort the results.[22] In addition, within the field of observational research, this type of study has less potential to provide evidence than cohort studies because it is uncontrolled. One potential source of bias is that patients who are dissatisfied with their current therapy tend to be satisfied with a switch to any other treatment, simply because it is different. Again, because participation is voluntary, the patients who

agree to be observed may be more inclined to report a greater analgesic effect; conversely, the inclusion of patients who have not responded well to their current therapy introduces the potential for selection of a cohort of patients who are disinclined to assess any treatment positively.[32]

Another potential source of bias is the number of patients lost to follow-up during the study. The proportion of withdrawals was much higher in this study (at 3 months, pain relief data were available for 56.2% of patients) compared with the premarketing trials of buprenorphine TDS (range, 7%–28%).[17–19] This is likely to have been the result of the longer duration of follow-up in the present study (3 months vs a maximum of 3 weeks) and the fact that in observational studies of routine clinical care, multiple factors affect patients' availability for follow-up. However, because the results of the observed-case and worst-case analyses were not significantly different, it appears that the effect of missing data was not substantial. In fact, investigators considered fewer than half of study withdrawals to be associated with an adverse event or with unsatisfactory pain relief.

Another limitation of this study is the absence of pain intensity data measured on a reliable visual analog scale. However, verbal rating scales were used to keep the study procedures as simple as possible to ensure minimal interference with routine practice. Moreover, the use of verbal rating scales provided data that could be compared with the results of premarketing clinical trials of buprenorphine TDS, which also used verbal rating scales. The Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain from the Committee for Proprietary Medicinal Products states that verbal rating scales correlate with visual analog scales in various settings.[33]

Finally, the exact proportion of outpatients to inpatients in the sample was not available. However, the results can be considered applicable to outpatients, as the hospitalized cases were only anecdotal.

CONCLUSIONS

In the present uncontrolled observational study conducted in clinical practice settings in Spain, buprenorphine TDS was effective and well tolerated in the treatment of chronic moderate to severe pain of malignant or nonmalignant origin. The effect was particularly evident in patients with cancer pain.

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