

**ORAL TRANSMUCOSAL FENTANYL CITRATE USE IN CHRONIC
NONCANCER PAIN: A RETROSPECTIVE SURVEY**

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INTRODUCTION

Chronic noncancer pain is frequently associated with significant physical disability that also impacts on the emotional and financial status of patients and their families.¹ Affecting millions of Americans, chronic noncancer pain is unpredictable and the most difficult type of pain to manage.^{2,3} Chronic pain can often be divided according to its temporal variations into persistent pain and breakthrough pain (BTP). BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.⁴ BTP is characterized by an unpredictable and rapid onset of pain that is moderate to severe in intensity and of relatively short duration.^{4,5} BTP is a well-recognized clinical problem in patients with cancer and is also experienced by patients with chronic noncancer pain conditions. Optimal management of BTP requires a medication with a rapid onset of analgesia and relatively short duration of action to match the trajectory of episodes of BTP.

Oral transmucosal fentanyl citrate (OTFC[®], ACTIQ[®]) is a novel, opioid product specifically designed to deliver rapid analgesia and developed for treating patients who experience BTP.⁶⁻⁹ OTFC is currently indicated for the management of BTP in opioid-tolerant patients with cancer pain.¹⁰ In a controlled study in postoperative patients, the onset of pain relief with OTFC was as rapid as with IV morphine – within 5-10 minutes.¹⁰ Relative potency studies have estimated OTFC to be approximately 10-20 times more potent than IV morphine.^{11,12} Accordingly, the analgesic effect of 200 mcg of OTFC would be comparable to that of 2-4 mg of IV morphine or 6-12 mg of oral morphine (assuming a 3:1 conversion rate for IV to oral morphine). Relative potency data for OTFC are useful

for choosing a starting dose but are not used to predict the successful dose of OTFC based on the dose of the long-acting opioid or to switch from one opioid to another.

OTFC is available in 6 dosage strengths, ranging from 200 mcg to 1600 mcg, enabling individualized patient dosing. The appropriate dose of OTFC is determined by titration, and the appropriate (“successful”) dose of OTFC is defined as the dose at which 1 unit provides adequate pain relief with acceptable side effects.⁶⁻⁹

Several controlled clinical trials have demonstrated that OTFC is effective and well tolerated for the management of BTP in cancer patients who are receiving chronic doses of around-the-clock opioids to control persistent pain.⁶⁻⁹ In a direct comparison, OTFC provided significantly better relief of BTP than oral morphine, and approximately 94% of patients preferred OTFC to oral morphine.⁹ In addition, pain management clinicians have begun to use OTFC in patients with chronic noncancer pain to help treat episodes of BTP. Recent reports have suggested that OTFC may have clinical utility in this population.^{11,13-15}

Progressive clinical experience has led to a broader acceptance of opioids in the treatment of noncancer pain. Indeed, a consensus document published by the American Academy of Pain Medicine and the American Pain Society advocates that clinicians should consider the use of opioids in selected patients for the management of chronic noncancer pain.¹⁷

Furthermore, recently published treatment guidelines have included opioid use in chronic noncancer pain conditions such as osteoarthritis and rheumatoid arthritis.¹⁸ The Federation of State Medical Boards has published model guidelines for the use of opioids in chronic noncancer pain that emphasize several key areas, such as patient evaluation, written treatment plans, informed consent and agreements for treatment, periodic reviews,

consultations, appropriate medical record documentation, and compliance with controlled substance laws and regulations.¹⁹ Consequently, patients with chronic noncancer pain are increasingly being prescribed long-acting opioids on a regularly scheduled basis to control persistent pain and short-acting opioids for flares of BTP.

We conducted a retrospective survey to gain insight into emerging practice patterns with OTFC in the management of chronic noncancer pain in 5 pain management practices. In addition, we sought to characterize the dose of OTFC at which titration was started and successful, the dose of OTFC at the follow-up visit, and the frequency at which OTFC dose adjustments were required over the course of treatment.

METHODS

Patients

The medical charts of 100 patients with chronic noncancer pain who had received OTFC were reviewed in this retrospective convenience sample survey. These patients were ≥ 18 years of age and had been on a stable OTFC dose for at least 2 weeks. Twenty patients were randomly selected from each of 5 pain management practices across 4 states—Florida (2 practices), Georgia, Utah, and California. Patient chart information from June 1999 to May 2003 was included. The age, sex, and primary pain diagnosis for each patient were recorded; however, no patient-specific identification information was documented.

OTFC dosing

The dates and OTFC dosage strengths were recorded for each patient at 3 clinic visits: at the first visit when OTFC was initially prescribed; at the visit after titration to a successful OTFC dose; and at the last (follow-up) visit. The successful OTFC dose was defined as the dose at which 1 OTFC unit provided adequate pain relief with acceptable side effects and with no change in the prescribed OTFC dosage strength over 2 consecutive clinic visits.

Concomitant medications

Concomitant analgesic and adjuvant analgesic medications were also recorded at the first and last clinic visit. Sustained-release oral opioids and transdermal fentanyl were classified as “long-acting” opioids. Normal-release opioids, including those combined with acetaminophen or other agents, were classified as “short-acting opioids”. OTFC was not included as a short-acting opioid in this analysis.

Pain scores

Although the primary purpose of this study was to identify the usage and dose titration patterns of OTFC and not to evaluate efficacy, pain intensity scores were also analyzed. Seventy-one of 100 patients rated pain intensity using an 11-point numerical scale (0=no pain to 10=worst pain imaginable). These scores were recorded at the first and last patient visit in 4 of the 5 pain clinics.

Statistical analyses

Summary descriptive statistics were calculated using an SPSS statistical software package.

The mean pain scores recorded at the first and last visit were compared using a paired samples *t* test, which was contained within SPSS.

RESULTS

Patients

Of the 100 patients in this retrospective survey, 64 were women (mean age, 45 years [range, 25-71 years]) and 36 were men (mean age, 52 years [range, 29-82 years]). The most common primary pain diagnoses reported were chronic back pain and headache (Figure 1). Six patients who transferred into 1 of the 5 clinics were already receiving OTFC but did not have information on their starting dose and successful dose. Therefore, these patients were excluded from the subsequent dose analyses. Another patient who was not on the same OTFC dose for 2 consecutive clinic visits was also excluded from the analyses.

Concomitant medications

Most patients reported taking multiple analgesics and combination analgesics at the first and last visits. Concomitant medication data for both first and last visits were available for 93 patients (Table 1). Only 4% and 2% of patients reported not taking any opioids at the

first and last visits, respectively. Other analgesics reported by >10% of patients at the first and last visit were, respectively, antidepressants, 60% and 68%; anticonvulsants, 38% and 48%; skeletal muscle relaxants, 38% and 44%; NSAIDs, 25% and 26%; and hypnotics, 14% and 18%.

Pain scores

OTFC reduced pain, as shown by the significant decrease in patients' mean pain intensity scores between the first and last visit (n=71; $P<0.01$) Mean (\pm SD) pain intensity scores decreased from 7.6 (\pm 2.7) prior to initiation of OTFC to 5.9 (\pm 2.7) at follow-up. This improvement in subjective pain ratings was also considered to be clinically significant.

OTFC dosing

The most common starting doses of OTFC for patients were 400 mcg and 800 mcg (Figure 2). The most common successful doses of OTFC were 400 mcg and 800 mcg (Figure 2). The mean length of time from starting OTFC to reaching a successful dose was 39 days (range, 3-286 days). At the last visit (follow-up), most patients (68%) were on the same dose of OTFC as their successful dose. At the last visit, the majority of patients (73%) were using 1-4 OTFC doses per day (<1 unit/day, 9%; 1-2 units/day, 39%; 3-4 units/day, 34%; >4 units/day, 18%). The mean length of time from reaching a successful dose to the last visit was 68 days (range 12-661 days).

DISCUSSION

OTFC is a novel convenient, non-invasive opioid delivery system specifically designed to provide rapid analgesia for the treatment of patients who experience BTP. OTFC has previously demonstrated efficacy and tolerability for the management of BTP in opioid-tolerant patients with chronic cancer pain.⁶⁻⁹ The results from our retrospective survey provide evidence that OTFC is also being successfully used in pain clinics for pain management in patients with chronic noncancer pain. The most common types of chronic pain diagnoses included in this survey were back pain and headache. Most patients (81%) were using long-acting opioids, yet many patients (70%) required short-acting opioids for pain management. In addition, use of non-opioid analgesic and adjuvant analgesic medications was also reported by patients in this survey suggesting that many of these patients had complicated pain problems.

The optimal dose of OTFC is individualized for each patient by titration, beginning at a low dose and aiming for the dosage strength at which 1 OTFC unit provides adequate pain relief with acceptable side effects. In this survey, 400 mcg was the most common starting dose of OTFC reported, with 800 mcg the next most common dose. The most common successful OTFC doses for patients were 400 mcg and 800 mcg. At follow-up, most patients (68%) remained on the same dose of OTFC at which successful titration had been achieved, indicating that analgesic tolerance was not a major problem in this patient group over the duration of this survey. This finding in patients with noncancer pain is consistent with the results from a recent long-term safety study in cancer patients using OTFC to

manage BTP.¹⁶ Also consistent with the use of OTFC in cancer patients,⁶⁻⁹ most of the patients in our survey (73%) were using 1-4 OTFC units per day.

The findings of this patient survey should be considered in light of the limitations of the design and methodology employed. The survey utilized a convenience sample of patients with chronic noncancer pain who had been successfully managed with OTFC, and the chart reviews were conducted at 5 sites, which may have varied in patient selection and treatment approaches. Since this was not a controlled intervention study, conclusions regarding the efficacy of OTFC in patients with chronic noncancer pain cannot be drawn. OTFC was generally well tolerated, and although adverse events were not recorded in a systematic manner on the patient charts, there were no reports of any serious adverse events. Further controlled studies are required to help define patient selection criteria and to determine the efficacy and tolerability of OTFC in patients with chronic noncancer pain. Nevertheless, the results of this survey are useful because they describe patients with various chronic noncancer pain conditions who were successfully managed with OTFC and indicate the dosage and titration approaches that were employed.

CONCLUSIONS

Based on the results of this retrospective survey, OTFC may be useful in the management of selected patients diagnosed with a variety of chronic noncancer pain disorders.

Furthermore, development of tolerance to the analgesic effects of OTFC did not appear to be a problem in this group of patients, and no serious adverse events were reported.

OTFC may offer a new, non-invasive and well-tolerated treatment option to rapidly deliver analgesia in patients with chronic noncancer pain.

ACKNOWLEDGEMENTS

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Table 1. Number of patients on short- or long-acting opioids, or a combination of both

Medication	First visit (n=93)	Last visit (n=93)
Long-acting opioid (%)	75 (81)	80 (86)
Short-acting opioid (%)	65 (70)	61 (66)
Short- and long-acting opioid (%)	51 (55)	50 (54)

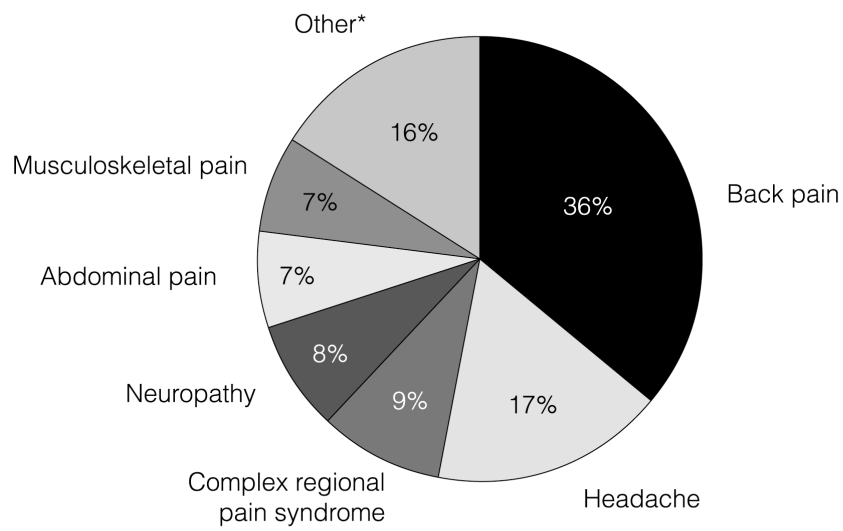
FIGURE LEGENDS

Figure 1. Primary pain diagnoses

Figure 2. Mean pain scores (\pm SEM) at first and last visit

Figure 3. OTFC starting and successful doses (n=93)

Figure 1



*Other includes: fibromyalgia, multiple sclerosis, sickle cell, pelvic and renal pain (<5% each)

Figure 2

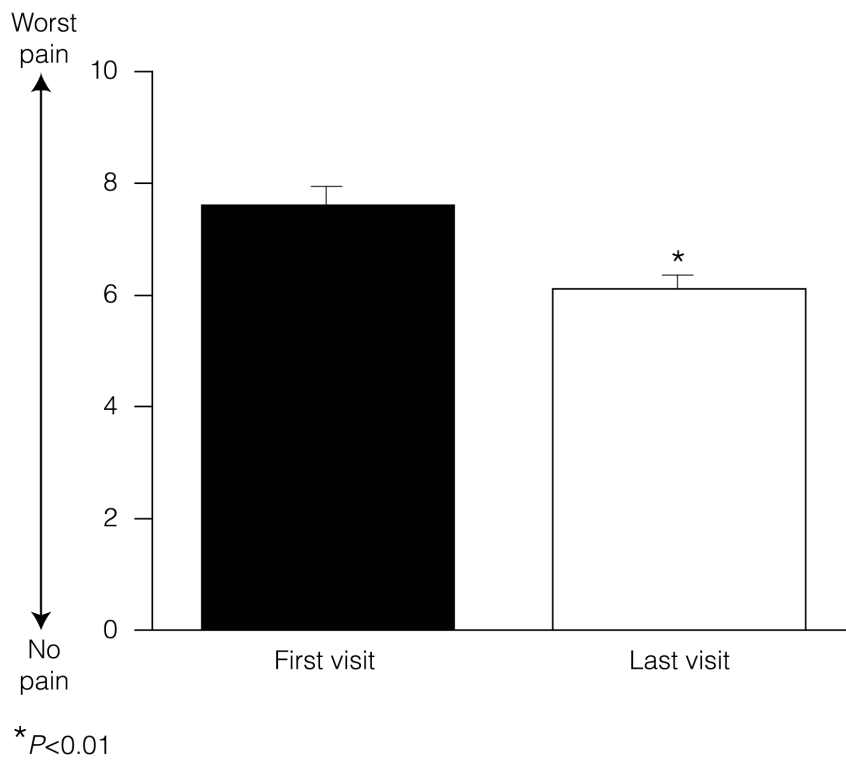
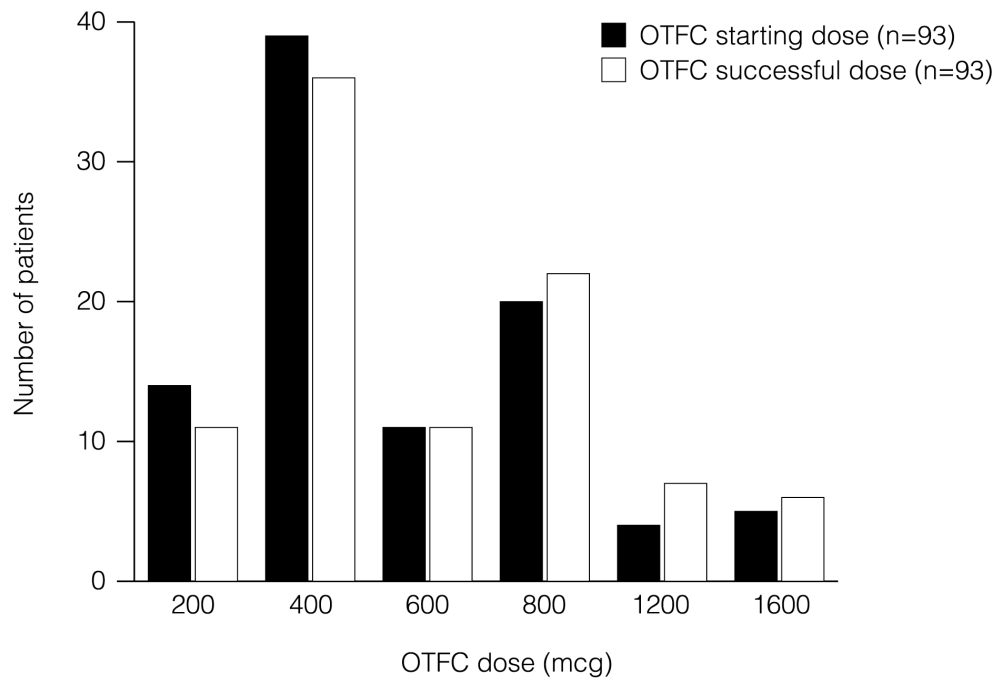


Figure 3



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TABLE 1. Concomitant opioid medications reported by patients with chronic noncancer pain

Medication	First visit (n=93)	Last visit (n=93)
Long-acting opioid, n (%)	75 (81)	80 (86)
Short-acting opioid, n (%)*	65 (70)	61 (66)
Both short-acting and long-acting opioids, n (%)*	51 (55)	50 (54)

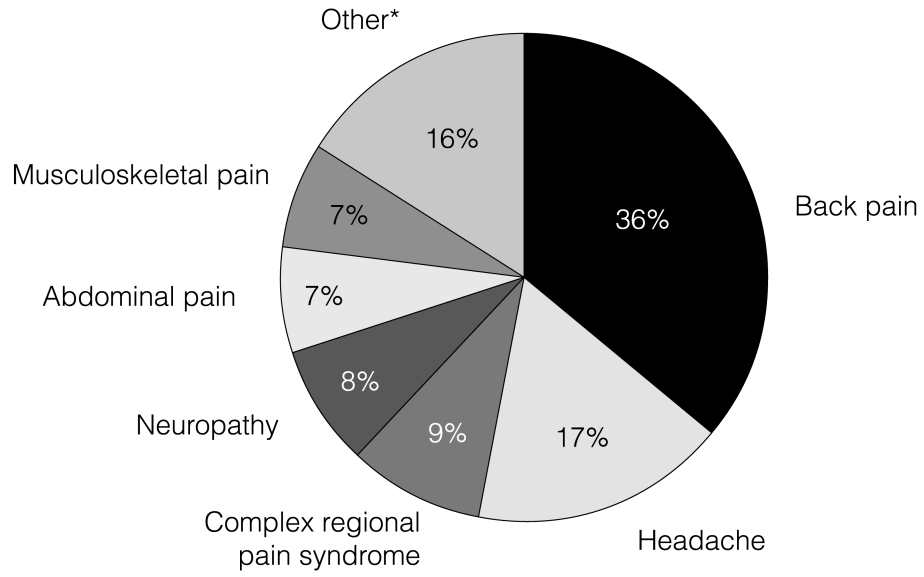
*OTFC was not included as a short-acting opioid in this analysis.

FIGURE LEGENDS

FIGURE 1. Primary pain diagnoses (N=100)

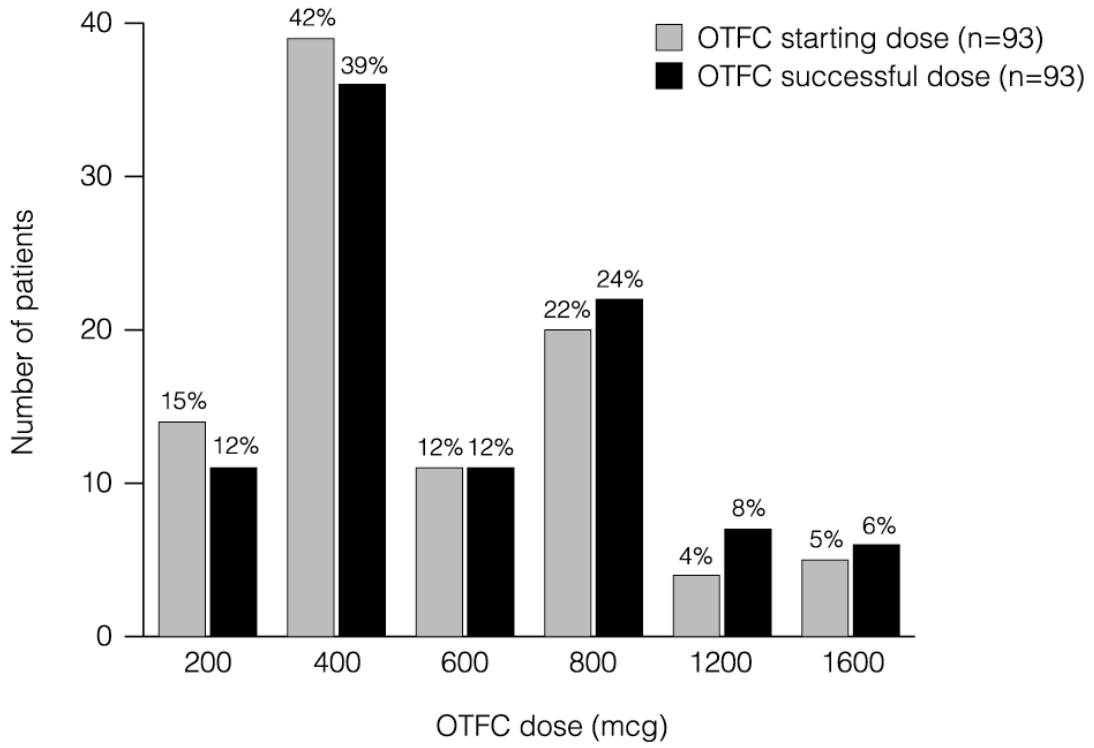
FIGURE 2. Starting and successful doses of OTFC (n=93)

Figure 1



*"Other" includes fibromyalgia, multiple sclerosis, sickle cell, pelvic and renal pain (<5% each)

Figure 2



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