An Alternative Algorithm for Dosing Transdermal Fentanyl for Cancer-Related Pain

ABSTRACT: Many cancer patients are undermedicated and inappropriately managed for pain, leading to a diminished quality of life. Patients with moderate to severe pain often require opioid analgesics. Recently published guidelines emphasize individualization of opioid treatment to provide the drug and route of administration that meet the needs of the particular patient. Intolerable side effects, ineffective pain relief, or a change in the patient’s clinical status can dictate the need for a new pain management regimen. Physicians must be able to readily quantify relative analgesic potency when converting from one opioid to another or from one route of administration to another. Transdermal fentanyl (Duragesic) is an opioid agonist that has been shown to be safe and effective for the treatment of cancer pain. However, clinicians should realize that the manufacturer’s recommendations for equianalgesic dosing of transdermal fentanyl may result in initial doses that are too low in some patients, and in a titration period that is too long. Under these circumstances, the patient is likely to experience unrelieved pain. An alternative dosing algorithm that considers both a review of the literature and our combined clinical experience with transdermal fentanyl should help clinicians individualize the treatment of pain. [ONCOLOGY 14(5):695-705, 2000]

Introduction

Pain associated with malignancy is a critical problem in cancer patients. The majority of patients (65% to 85%) with advanced disease and at least one-third of newly diagnosed patients report pain.[1-4] Although approximately 90% of patients with cancer pain can be effectively treated with an integrated program of non-pharmacologic, pharmacologic, and anticancer therapies, a significant number of cancer patients are undermedicated and inappropriately managed, resulting in suboptimal pain control.[4-6]

Appropriate pain management requires proper pain assessment followed by a targeted approach to pain control.[4,7] A thorough assessment of an individual cancer patient’s etiology of pain, age, extent of disease, previously effective and ineffective therapies, concurrent medical problems, and psychosocial status is required to select the best approach. Each patient’s plan of care must be individualized, reassessed, and, if necessary, altered regularly to maximize pain control, functionality, and ultimately, quality of life. The patient’s self-report of pain should be the basis of pain management, since both caregivers and health care workers tend to underestimate pain severity.[4]

According to guidelines published by the World Health Organization, the choice of analgesic should be based on the intensity of pain reported by the patient, rather than its specific etiology.[8] Patients with mild pain may benefit from nonopioid agents, including aspirin, acetaminophen, ibuprofen, or other nonsteroidal anti-inflammatory drugs.

If mild to moderate pain is not adequately relieved with optimally used nonopioid analgesics, or if nonsteroidal medications are contraindicated, opioid analgesics should be considered. At this point, opioids can be used alone or in combination with nonopioid therapies. Adjuvant agents, such as corticosteroids, tricyclic antidepressants, and anticonvulsants, can be used concurrently to enhance analgesic efficacy, treat opioid-induced symptoms or to alleviate specific types of pain. Persistent or recurrent pain requires treatment with a regularly scheduled regimen.[4] However, even patients whose pain is generally well managed with around-the-clock dosing experience
Episodes of “breakthrough” pain resulting from activity, stress, or disease progression. When this occurs, patients require agents that provide a rapid onset of action and short duration of effect to complement the pain-control regimen.[4] When breakthrough pain occurs regularly, an increase in the dose of the currently prescribed medication or the use of a different analgesic or a different delivery system may be needed.[4,9,10]

Uncontrolled pain diminishes the quality of life of cancer patients. Cancer pain and its treatment may exacerbate other symptoms of cancer, including fatigue, weakness, dyspnea, nausea, constipation, and impaired cognition.[1,2] Patients with pain hesitate to participate in normal daily activities for fear of worsening the pain. Social and family relationships may suffer as patients avoid interpersonal interaction or experience personality changes as a result of persistent pain.

Conversion Issues for Opioids

Recently, a number of experts and organizations have developed guidelines for the treatment of pain. Although initially the “step” approach was recommended,[8] more recent guidelines emphasize individualization of therapy, advocating selection of the appropriate drug and route of administration for each patient.[11-14]

During the course of cancer pain management, patients frequently require a change from one opioid to another. A different opioid may be necessary as a result of intolerable side effects, cost considerations, or the need for an alternative route of administration as the patient’s disease progresses.

In an attempt to quantify the frequency with which experienced clinicians make treatment changes in response to the changing clinical status of cancer patients, Cherny et al conducted a prospective survey of 100 patients referred to the Pain Service at Memorial Sloan-Kettering Cancer Center over a 14-week period.[15] Of the 100 patients, 99 had received therapy with a median of 2 different opioids (range, 1 to 8) administered by a median of two different routes (range, 1 to 8).

After initial evaluation, the Pain Service physicians changed the opioid or route of administration in 58 patients. Of the 42 patients whose medication was unchanged at initial evaluation, 22 required subsequent changes in either drug or route of administration. Thus, 80 patients required changes in drug or route of administration prior to death or discharge. These 80 patients experienced a total of 182 changes in drug and/or route of administration.

Frequent changes between different drugs and different routes of administration require physicians to readily quantify relative analgesic potency when changing from one opioid to another or one route of administration to another, so that pain control can be maintained and side effects minimized.[16,17] TABLE 1

| TABLE 1 | Equianalgesic Potency Conversion |

When a change in opioids is required, physicians often refer to conversion tables published in textbooks or guidelines. Conversion tables are often based on the results of single-dose studies in patients receiving low opioid doses for postoperative pain. Although relative analgesic potency is conventionally expressed in comparison with 10 mg of parenteral morphine or 60 mg of oral morphine (Table 1),[11,18] many recent studies have reported that the standard conversion tables underestimate the potency of opioids in patients who are receiving repeated doses.[19,20]

Opioid Agents

Based on their interactions with the various receptor subtypes, opioid agents can be divided into four classes: pure agonists, partial agonists, agonist-antagonists, and pure antagonists. Pure agonists are used most commonly in the treatment of cancer pain.

Agents in this class include codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol (Levo-Dromoran), meperidine, methadone, morphine, oxycodone, and oxymorphone.
(Numorphan). Pure agonists bind completely to mu receptors and usually do not have a ceiling dose. The dose is increased as necessary to allow for adequate analgesia unless intolerable or unmanageable side effects occur.[21]

**Transdermal Fentanyl**

Fentanyl, like other opioids, exerts its principal pharmacologic effects on the central nervous system. Fentanyl is approximately 75 times more potent than morphine on a molar basis.[22] Transdermal fentanyl (Duragesic) is a system that provides continuous systemic delivery of fentanyl. In the transdermal system, fentanyl is released from a cutaneously applied reservoir at a nearly constant amount per unit of time. The amount of fentanyl released per hour is directly proportional to the surface area of the patch in contact with the skin. Commercially available patch sizes provide delivery rates of 25, 50, 75, and 100 µg/h.

Following patch application, fentanyl initially concentrates in the upper skin layers before it becomes available to the systemic circulation.[23] Serum fentanyl concentrations level off between 12 and 24 hours after the first application.[24] With continuous use, serum fentanyl levels reach and maintain a steady state after the second dose, and fluctuations of serum levels are minimal after the first 72 hours. This allows for a constant level of analgesia.

Although about 40% of the fentanyl remains in the gel matrix in the patch after 72 hours, the gradient across the skin is too low to maintain adequate diffusion of fentanyl after this time. After removal, serum fentanyl levels decrease gradually, about 50% in 17 hours (range, 13 to 22 hours).

**TABLE 2**

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<th>Clinical Trials Assessing Transdermal Fentanyl in the Management of Cancer Pain</th>
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**Studies in Cancer Pain**—The transdermal route has been the most extensively studied method of administration of fentanyl in cancer patients. Several nonblinded clinical studies have shown that transdermal fentanyl effectively controls chronic pain associated with cancer. Therapy was converted from stabilized morphine doses to transdermal fentanyl generally without loss of pain relief.[25] Table 2 summarizes the results of these trials.[26-32] In addition, two studies have assessed quality of life and patient preference. In one study of 202 cancer patients who required strong opioids for pain, significantly more patients preferred transdermal fentanyl to sustained-release oral morphine (P = .037). This preference may have been related to the fact that transdermal fentanyl was associated with less constipation (P < .001), less daytime drowsiness (P = .015), and less disruption to daily life (55% in fentanyl-treated patients vs 20% in morphine recipients).[26] These data were recently confirmed in a trial assessing quality of life and satisfaction with transdermal fentanyl vs oral morphine.[33] Again, patients receiving transdermal fentanyl were more satisfied overall with their pain medication than were patients receiving sustained-release oral morphine. This may have resulted from the significantly lower frequency (P < .002) and severity (P < .001) of side effects. There were no significant differences between treatment groups with respect to measures of pain intensity, sleep adequacy, or symptoms. Although these studies were not randomized, controlled trials and the interpretation of the data is confounded by the concomitant use of rescue doses of opioids, they nonetheless provide consistent data on pain relief and side effects in large numbers of patients managed with oral morphine or transdermal fentanyl.

**Patient Acceptance and Side Effects**—In general, transdermal fentanyl is well accepted by cancer patients, leading to excellent compliance with the prescribed regimen. Transdermal fentanyl is noninvasive, and analgesia is sustained for long durations. This therapy can be administered to patients who cannot take oral analgesic medications because of such cancer-related side effects as
nausea, vomiting, and dysphagia. Like other opioids, transdermal fentanyl has been reported to produce adverse reactions during both clinical trials and postmarketing studies. The most serious reactions were deaths due to hypoventilation resulting from inappropriate use.[32] Specifically, use of a patch size greater than 25 µg/h in opioid-nave patients or those with acute self-limited pain (eg, acute dental pain) is contraindicated. Hypotension and hypertension were observed in opioid-nave patients. The most common side effects seen with transdermal fentanyl include sedation, nausea, vomiting, and constipation. However, an open multicenter study of 40 cancer patients requiring opioid analgesia suggested that transdermal fentanyl may result in less nausea, vomiting, and constipation than does morphine.[27]

**Dosing of Transdermal Fentanyl**

**Manufacturer's Recommendations**

To convert therapy from oral or parenteral opioids to transdermal fentanyl, the manufacturer recommends the following steps[32]: (1) Calculate the previous 24-hour analgesic requirement. (2) Convert this amount to the equianalgesic oral morphine dose (Table 1). (3) Determine the calculated 24-hour oral morphine dose and the corresponding transdermal fentanyl dose (Table 3). (4) Initiate treatment using this recommended dose, and titrate dosage upward (no more frequently than every 3 days after administering the initial dose or every 6 days thereafter) until analgesic efficacy is attained. Maximal efficacy cannot be determined for at least 24 hours after initial patch placement, and dosage adjustment can take up to 6 days. Titration of the transdermal fentanyl dose considers the daily dose of supplemental analgesics required by the patient during the second and third days after initial patch application.

**Clinical Impact of Manufacturer's Recommendations**—The manufacturer’s recommendations for dosing transdermal fentanyl are based on experience gained from clinical trials. However, more than 7 years of use of the drug in clinical practice suggests that at least half of the patients who receive transdermal fentanyl after being exposed to other opioids are initially underdosed.[25] In these patients, use of dosing tables based on the 6:1 ratio of oral to parenteral morphine may result in underestimation of the dose when converting from oral morphine to transdermal fentanyl and overestimation when switching from the patch to oral morphine.[34]

If the initial dosage is too low, the subsequent dose titration of transdermal fentanyl, as recommended, can take days. Patients and physicians faced with inadequate pain relief for up to 6 days often discontinue the drug before an effective dose is reached. This is typically more of a problem in patients with chronic pain who have been exposed to opioids previously and therefore require higher doses of opioids to control their pain. Opioid-nave patients typically need fewer dose increments to reach an appropriate dose.

The literature contains four case reports of withdrawal syndromes associated with conversion from oral opioids to transdermal fentanyl. These cases were not related to psychological dependence, but rather, to the physical effects of too low an estimated equianalgesic dose.[35,36] Therapeutic levels of fentanyl can take 12 to 18 hours to occur after initial patch application. Patients at greatest risk for withdrawal are those who are physically dependent and who stop taking oral opioids prior to the first application of the transdermal patch and/or prior to the achievement of steady-state fentanyl
Alternative Dosing Algorithm

FIGURE 1

Alternative Dosing Algorithm for Transdermal Fentanyl

Dosing of transdermal fentanyl that is too conservative results in suboptimal use of this drug. Patient care can be compromised as patients experience uncontrolled pain during the initial conversion and titration period. An alternative algorithm based on the authors’ clinical experience in treating cancer pain with this proven agent and a review of the literature should aid clinicians in achieving proper pain management with transdermal fentanyl (Figure 1).

**Recommendation 1: Converting to Transdermal Fentanyl**—In cancer patients with chronic pain who have been treated previously with opioids, 60 mg/d (600 mg/d) of oral morphine is equianalgesic to 25 µg/h of transdermal fentanyl. Table 4

Based on the consensus of expert clinicians, this can easily be remembered as a conversion ratio of approximately 2:1 (oral morphine to transdermal fentanyl) to obtain an approximate starting dose of transdermal fentanyl (Table 4).[11] Extreme caution must be exercised to ensure that a morphine dose expressed as mg/d is converted to a transdermal fentanyl dose expressed as µg/h.

Once an approximate starting dose is calculated, round up or down to the available patch strength based on the clinical status of the patient. If the patient is obtaining adequate pain relief from the currently prescribed medication, start at the lower patch size (as illustrated in Case Report 1). If the currently prescribed medication is not offering sufficient efficacy, round up to the nearest patch strength (as illustrated in Case Report 2).

**Case Reports: Determining the Appropriate Initial Fentanyl Patch Size**

**Case Report 1**: Patient A is deriving good pain relief from oxycodone (5 mg) plus acetaminophen (325 mg), 2 tablets every 4 hours, but would prefer not to take medication every 4 hours. To determine the dose conversion to initiate treatment with a transdermal fentanyl patch, convert the total daily oxycodone dose (5 mg × 2 × 6 = 60 mg/d) to an equianalgesic dose of oral morphine (120 mg/d). Using the 2:1 ratio described above, the dose conversion to transdermal fentanyl is roughly 60 µg/h. The nearest approximation for an initial conversion dose for a patient with relatively good analgesic control is transdermal fentanyl, 50 µg/h every 72 hours.

**Case Report 2**: Patient B is not obtaining adequate pain relief from a regimen of 12 mg/d of hydromorphone. You wish to convert the therapy to transdermal fentanyl. The hydromorphone is equianalgesic to a dose of 96 mg/d of oral morphine. A 2:1 ratio suggests a patch strength of 48 mg/h. Round up to and begin treatment with transdermal fentanyl using a patch size of 50 µg/h.

The safety and analgesic efficacy of the recommended 2:1 ratio is supported by a multicenter trial conducted by Donner et al.[37] In this study, therapy in 98 patients with cancer-associated pain was converted directly from oral morphine to transdermal fentanyl. The initial fentanyl dose was determined by the dose of sustained-release morphine used by each patient prior to the study period. The conversion ratio was very similar to the 2.5:1 ratio recommended based on the...
alternative algorithm. For example, patients receiving 30 to 90 mg/d of oral morphine were initially
dosed with a 25-µg/h patch; patients receiving 91 to 150 mg/d oral morphine received a 50 µg/h
patch; and so forth. Patients were permitted to use supplemental liquid morphine during the study
period to attain sufficient analgesia.

Pain relief during treatment with transdermal fentanyl was similar to that with sustained-release
morphine, but significantly more patients required supplemental medication while receiving fentanyl.
Constipation was less problematic in patients treated with fentanyl. Vital signs and the incidence of
side effects were the same. Respiratory depression was not seen; however, three patients developed
the morphine withdrawal syndrome within the first 24 hours of transdermal fentanyl therapy. The
highest dose of transdermal fentanyl administered was 500 µg/h.

Although some authors have proposed the use of parenteral fentanyl as an intermediate step in
converting from opioids to transdermal fentanyl, this approach is not cost-effective or convenient for
outpatients and, therefore, is not recommended.[38-40]

**Recommendation 2: Titrating Transdermal Fentanyl**—Physicians should determine whether the
dose of the patch is sufficient for optimal pain management after 24 to 30 hours and always by 72
hours. If the patient requires more than three doses of breakthrough medication daily to obtain
adequate pain relief, the patch dose should be increased.

Determination of the optimal dose of transdermal fentanyl should be based on an ongoing evaluation
of the level of pain relief achieved and the requirement for breakthrough medications. It takes
approximately 14 hours (range, 12 to 18 hours) to reach clinically relevant plasma levels after the
initial patch of transdermal fentanyl is applied.[41] Constant serum levels are achieved after 16 to
20 hours, and steady state is attained at about 72 hours.

At low doses of opioids, the dose of the patch is normally increased in increments of 25 µg/h. It may
be increased in increments of 50 µg/h or higher, depending on the severity of the pain, number of
breakthrough doses required, and total dose of transdermal fentanyl used. TABLE 5

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| Recommendation 3: Treating Breakthrough Pain During Titraton—During the titration period, the patient should be instructed to use medication for breakthrough pain every 3 to 4 hours. Because transdermal fentanyl does not reach steady-state serum levels for 72 hours, to obviate withdrawal physicians should prescribe the previously used opioid at a minimum of 25% of the dose that the patient received during the previous 24 hours (Table 5).

As an example, if a patient is applying a 50-µg/h fentanyl patch every 72 hours, the equivalent daily oral dose of oxycodone is approximately 60 mg. During the initial 18 hours following application of the patch, the patient should be instructed to take at least 15 mg (25% of 60 mg) of oxycodone until steady-state serum fentanyl levels are achieved. This practice must be differentiated from breakthrough medication, since the patient should take at least 15 mg of oxycodone to abate development of withdrawal symptoms during this phase regardless of whether breakthrough medication is required.

Principles for treating breakthrough pain include the use of agents that are simple to administer,
offer rapid pain relief, and have a reasonably short half-life.[42] Patients using transdermal fentanyl can continue taking the short-acting opioid that was previously effective for breakthrough pain.[42] Many patients who are receiving transdermal fentanyl take immediate-release morphine, hydromorphone, or oxycodone as their rescue medication.[42]

**Recommendation 4: Long-Term Treatment of Breakthrough Pain**—After a steady state of
fentanyl has been reached, ideally patients should be taking no more than three doses of
breakthrough medication daily. If breakthrough pain is persistent and frequent, the physician should
increase the baseline dose of transdermal fentanyl by 25% to 50%. Patients whose pain is well
controlled for the first 48 hours and who require additional doses of breakthrough medication more
often during the third day should have a new patch, at the same dose, applied every 48 hours.

A common method of treating breakthrough pain is to use 5% to 15% of the previous 24-hour opioid
dose administered at 3- to 4-hour intervals.[21] Several authors routinely increase the 24-hour
fentanyl dose to 25% of the previous 24-hour opioid, and have reported no serious adverse effects using this approach. Patients who require an increase in the dose of the around-the-clock medication as a result of disease progression or other factors should be given an equivalent increase in the dose of the breakthrough pain medication.

**Recommendation 5: Frequency of Patch Application**—If a patient requires more than four doses of breakthrough pain medication over the 24-hour period between the second and third day following patch application, a new fentanyl patch is advised. Changing fentanyl patches more often than every 48 hours is not recommended.

As mentioned above, the analgesic effect of transdermal fentanyl begins approximately 12 hours after the patch is first applied. Analgesia peaks in 20 to 28 hours and usually lasts for 72 hours.[24] At steady state, more than 80% of the total dose is absorbed within 48 hours.[23] Thus, in many patients, the analgesic effect lasts for 72 hours; however, some patients may find that the effect begins to decline after 48 hours, usually at around 60 hours.

Fentanyl is delivered to the systemic circulation from the transdermal patch by diffusion from a higher to a lower concentration gradient. As the two concentrations become closer, the system becomes less efficient and less fentanyl is delivered, especially during the last 48 to 72 hours after patch application.

**Recommendation 6: Dosing for Opioid-Nave Patients**—Transdermal fentanyl can be used in opioid-nave patients with moderate to severe pain that is persistent or chronic. The transdermal fentanyl dose in these patients should be 25 µg/h. A short-acting opioid, such as hydrocodone (5 mg every 4 hours), should be added for breakthrough pain.

In general, transdermal fentanyl is not recommended in opioid-nave patients with acute pain syndromes, such as those associated with outpatient surgical procedures or other medical procedures (eg, dental extractions). Special care should be exercised when recommending fentanyl for frail or elderly patients or for opioid-nave patients with significant underlying chronic obstructive pulmonary disease or hepatic or renal disease.

### Misconceptions Regarding Opioid Use

**TABLE 6**

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<th>Concerns Regarding Use of Opioids</th>
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As a result of continued misperceptions among health care professionals about the nature of pain and its treatment with opioid agents, pain continues to be treated inadequately, leading to needless suffering among cancer patients. There is a reluctance to use available opioids because of concerns about physical dependence, addiction, tolerance, respiratory depression, and other side effects. However, we have found that these concerns do not typically apply to cancer patients with chronic pain, as outlined in Table 6.[11,32]

### Conclusions

The treatment approach outlined in this article is designed to facilitate the use of transdermal fentanyl for the management of cancer-related pain. The manufacturer’s recommendations for initial dose selection and dose titration were developed to ensure the safety of patients who receive this drug. Our experience in clinical practice has demonstrated that when dose selection and titration are too conservative, patient care is adversely affected.

Patients given too low a dose of transdermal fentanyl may experience uncontrolled pain, require too much breakthrough medication, or prematurely discontinue use of the drug because it takes too long to reach an effective dose. A more aggressive approach to dose escalation may remedy some of these problems. We believe that taking care to individualize each patient’s pain management will substantially reduce the undertreatment of cancer-related pain and its associated negative impact...
on patients’ quality of life.

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