REVIEW ARTICLE

Drug Safety 2003; 26 (13): 951-973
0114-5916/03/0013-0951/$30.00/0

Benefit-Risk Assessment of Transdermal Fentanyl for the Treatment of Chronic Pain

Craig A. Kornick, Juan Santiago-Palma, Natalia Moryl, Richard Payne and *Eugenie A.M.T. Obbens*

Department of Neurology, Memorial Sloan-Kettering Cancer Center, Pain and Palliative Care Service, New York, New York, USA

Contents

Abstract

Transdermal fentanyl is effective and well tolerated for the treatment of chronic pain caused by malignancy and non-malignant conditions when administered according to the manufacturer's recommendations. Compared with oral opioids, the advantages of transdermal fentanyl include a lower incidence and impact of adverse effects (constipation, nausea and vomiting, and daytime drowsiness), a higher degree of patient satisfaction, improved quality of life, improved convenience and compliance resulting from administration every 72 hours, and decreased use of rescue medication. Transdermal fentanyl is a useful analgesic for cancer patients who are unable to swallow or have gastrointestinal problems.

Transdermal fentanyl forms a depot within the upper skin layers before entering the microcirculation. Therapeutic blood levels are attained 12–16 hours after patch application and decrease slowly with a half-life of 16–22 hours following removal. Patients with chronic pain should be titrated to adequate relief

with short-acting oral or parenteral opioids prior to the initiation of transdermal fentanyl in order to prevent exacerbations of pain or opioid-related adverse effects. Transdermal fentanyl can then be initiated based on the 24-hour opioid requirement once adequate analgesia has been achieved.

The prolonged elimination of transdermal fentanyl can become problematic if patients develop opioid-related adverse effects, especially hypoventilation. Adverse effects do not improve immediately after patch removal and may take many hours to resolve. Patients who experience opioid-related toxicity associated with respiratory depression should be treated immediately with an opioid antagonist such as naloxone and closely monitored for at least 24 hours. Because of the short half-life of naloxone, sequential doses or a continuous infusion of the opioid antagonist may be necessary. Transdermal fentanyl should be administered cautiously to patients with pre-existing conditions such as emphysema that may predispose them to the development of hypoventilation.

Transdermal fentanyl is indicated only for patients who require continuous opioid administration for the treatment of chronic pain that cannot be managed with other medications. It is contraindicated in the management of acute and postoperative pain, as pain may decrease more rapidly in these circumstances than fentanyl blood levels can be adjusted, leading to the development of life-threatening hypoventilation.

Cognitive and physical impairments such as confusion and abnormal co-ordination can occur with transdermal fentanyl. Therefore, patients should be instructed to refrain from driving or operating machinery immediately following the initiation of transdermal fentanyl, or after any dosage increase. Patients may resume such activities once the absence of these potential adverse effects is documented.

Opioid analgesics are frequently administered for the treatment of acute, postoperative and chronic pain. Many patients can achieve adequate pain relief with immediate-release opioids; however, the need to take such medications every 3–4 hours can become extremely burdensome. The use of long-acting opioid preparations such as transdermal fentanyl for the treatment of chronic pain often results in improved analgesia, greater patient compliance, increased convenience, fewer adverse effects and an improved quality of life.[1-4] More predictable serum opioid levels may also be achieved with the use of long-acting preparations and can result in less reinforcement of drug-taking behaviours.

The purpose of this review is to familiarise readers with the pharmacology of, and clinical experience with, transdermal fentanyl and the benefits and risks associated with its use.

1. Pharmacology

Fentanyl is a synthetic opioid in the phenylpiperidine series. The drug functions primarily as a μ opioid receptor agonist and is estimated to be 80 times more potent than morphine as an analgesic.[5] Fentanyl is a highly lipophilic drug and is rapidly transferred across the blood-brain barrier into the CNS.[6] Fentanyl provides short-acting analgesic effects when administered intermittently by the oral, subcutaneous or intravenous routes.[7]

Fentanyl is well suited for transdermal administration because of its lipid solubility, high potency and low molecular weight (286 g/mol). These properties make it possible for therapeutic doses of fentanyl to be absorbed through a relatively small area of the skin. The noninvasive transdermal system that provides controlled systemic delivery of fentanyl for up to 72 hours was introduced in 1991

in the US. The administration of transdermal fentanyl has been described as an effective and well-tolerated treatment for malignant and non-malignant chronic pain.[8-14]

1.1 Transdermal Delivery System

Fentanyl administered using the transdermal delivery system is absorbed through a rate-limiting membrane by passive cutaneous diffusion.[15] Drug release is driven by the concentration gradient that exists between the saturated fentanyl solution in the patch reservoir and the lower concentration in the skin. Under normal physiological conditions, the rate-limiting membrane releases fentanyl onto the skin surface more slowly than the drug is absorbed into cutaneous tissue and the microcirculation. For this reason, overall control of fentanyl absorption is dictated by the design of the transdermal system rather than skin permeability, which can vary among patients. The rate-limiting membrane reduces the effects of interpatient variation in cutaneous permeability by approximately 50%.[16]

Transdermal fentanyl patches are composed of a removable protective liner and four layers: (i) a backing layer composed of a clear polyester film that serves as a physical barrier to prevent loss of fentanyl and excipients into the environment; (ii) a 3-day reservoir of fentanyl dissolved in alcohol and gelled with hydroxyethyl cellulose to enhance absorption; (iii) the rate-controlling membrane, composed of an ethylene-vinyl acetate copolymer film, that controls the rate of fentanyl delivery onto the skin surface; and (iv) a fentanyl-containing silicone adhesive layer that facilitates attachment to the skin, permits free passage of drug and releases a loading dose of drug upon initial application. The protective liner shields the adhesive layer prior to application and should be removed prior to use of the patch (figure 1).[15]

The release of fentanyl from the transdermal system is characterised by two distinct phases following initial application. During the first phase, a rapid loading dose is absorbed from the contact adhesive. This is followed by a plateau phase in which fentanyl is released from the patch reservoir at a constant rate.[18] Transdermal delivery eliminates gastrointestinal absorption and first-pass metabolism. For these reasons, lower drug dosages may be used, which results in a reduced incidence of adverse effects and less gastric irritation.[19]

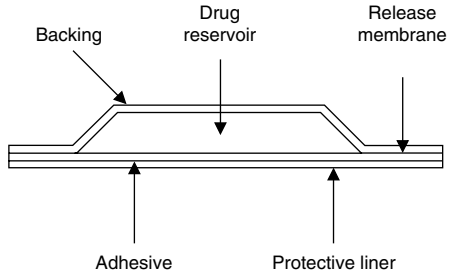

Fig. 1. Cross-section of a transdermal fentanyl delivery system (from Janssen Pharmaceutica,[17] with permission).

Transdermal patches are commercially available in four different sizes, which correspond to continuous delivery rates of 25 μg/hour, 50 μg/hour, 75 μg/hour and 100 μg/hour (table I). The surface area of the transdermal system in contact with the skin is directly proportional to the amount of fentanyl released into the cutaneous tissue and ultimately into the systemic circulation (25 μg/hour per 10 cm^2).[16] Multiple transdermal systems can be used to attain delivery rates greater than 100 μg/hour. Transdermal absorption of fentanyl is essentially the same between the chest, abdomen and thigh.[16,20] Each system contains 0.1mL of alcohol per 10 cm^2 to enhance the rate of drug flux through the rate-limiting membrane and to increase the permeability of the skin to fentanyl. Less than 0.2mL of alcohol is released from any sized transdermal system during regular use. The remaining components of the patch are pharmacologically inactive.

Table I. Structure and composition of transdermal fentanyl delivery systems[17]

Delivery rate[a] (μg/h)	Size (cm^2)	Fentanyl content (mg)
25	10	2.5
50[b]	20	5
75[b]	30	7.5
100[b]	40	10

a Nominal delivery rate per hour.

b For use only in opioid-tolerant patients.

Skin temperature and peripheral blood flow do not have a significant effect on fentanyl absorption under normal physiological conditions.[15,21] However, a pharmacokinetic model suggests that fentanyl blood levels could theoretically increase by approximately 33% if body temperature were to rise to 40°C (104°F) because of a temperature-dependent increase in fentanyl release and/or increased skin permeability.[22]

1.2 Pharmacokinetics

Fentanyl is a lipid-soluble drug that forms a depot within the upper skin layers and is then slowly released into the microcirculation when administered by the transdermal route. As a result, the administration of transdermal fentanyl is associated with delayed pharmacokinetics.[18,23] Absorption of fentanyl into serum occurs at a nearly constant rate and begins approximately 4–8 hours after the initial application of the transdermal system. However, therapeutic fentanyl blood levels are not achieved for approximately 12–16 hours.[18,23-25] Several studies have reported a delay between patch application and peak fentanyl blood levels that ranges from 17 hours to 48 hours.[26-29] Pain relief is therefore delayed for many hours following the initiation of transdermal fentanyl or an increase in dosage.[30] For this reason, transdermal fentanyl should not be used as a treatment for acute pain or for acute exacerbations of chronic pain that require opioid therapy. Instead, such patients should be titrated to relief with short-acting oral or parenteral opioids; initiation or dosage adjustment of transdermal fentanyl for long-term therapy may then be considered.[31]

Each transdermal system is labelled with a nominal flux that represents the average amount of drug delivered into the systemic circulation each hour; however, the actual rate of fentanyl delivery varies during the 72-hour application period. There appears to be considerable variability in the actual delivery rates and steady-state blood levels achieved among different patients treated with patches of the same nominal strength.[24,25,30] These differences are due to interpatient variability in both skin permeability and fentanyl clearance.[18] Gourlay et al.[24] reported significant discrepancies in delivery rates when nominal 50 μg/hour (actual range 29–76 μg/hour) and 75 μg/hour (actual range 48–213 μg/hour) patches were applied to different patients. Despite interpatient variability in skin permeability, differences in fentanyl clearance have the greatest influence on fentanyl blood levels.[15] As a result, it is difficult to predict peak plasma concentrations for individual patients. Fentanyl has a narrow therapeutic range (0.6–3.0 μg/L) and adverse effects increase in frequency at blood levels above 2 μg/L. Minimum effective and toxic concentrations rise as tolerance to fentanyl develops; however, the development of tolerance varies widely among patients. The goal of transdermal therapy is to maintain fentanyl blood levels within a range that produces adequate analgesia without dose-limiting adverse effects.

Portenoy et al.[30] have suggested that steady-state fentanyl blood levels are achieved approximately 72 hours after the initiation of transdermal fentanyl and remain stable with repeated administration. Steady-state blood levels are linearly proportional to the nominal delivery rate of transdermal fentanyl. However, steady-state levels vary between patients because of individual differences in absorption characteristics and fentanyl clearance rates.[14] At steady state, transdermal fentanyl produces sustained fentanyl blood levels similar to those provided by a continuous intravenous infusion with the same delivery rate.[23,24,32] A bioavailability study showed that 92% of the fentanyl dose delivered from transdermal patches reaches the systemic circulation.[18] This suggests that the fentanyl is not significantly degraded by the skin flora or cutaneous metabolism.

Fentanyl continues to be systemically absorbed from the cutaneous depot following removal of the transdermal delivery system(s).[23,24] For this reason, fentanyl blood levels decrease more slowly after the discontinuation of transdermal fentanyl compared with after the discontinuation of an intravenous infusion of fentanyl. Blood levels slowly decline to approximately 50% within 16–22 hours following the removal of transdermal fentanyl,[18,23,24,32] compared with a half-life of 6.1 hours for intravenous

fentanyl.[18] Cases of blood levels rising immediately after patch removal have also been reported.[24,33] However, mean total body clearance of fentanyl following patch removal is similar to that for intravenous fentanyl. This suggests that the slow decay time associated with transdermal fentanyl is probably the consequence of a cutaneous depot effect rather than a lower clearance rate.[24]

The prolonged elimination phase of transdermal fentanyl can become extremely problematic if patients develop opioid-related adverse effects, especially hypoventilation. Adverse effects should not be expected to improve immediately after patch removal and may take many hours to diminish. Patients who experience toxicity associated with respiratory depression should be immediately treated with an opioid antagonist such as naloxone and closely monitored for at least 24 hours. The duration of hypoventilation following an overdose may last longer than the effects of the opioid antagonist, as the half-life of naloxone ranges from 30 to 81 minutes. Therefore, patients may require sequential doses or a continuous infusion of an opioid antagonist.[18,28,30]

Fentanyl is primarily metabolised by the human cytochrome P450 (CYP) 3A4 isoenzyme system.[34] In humans, fentanyl appears to be mainly metabolised by oxidative *N*-dealkylation to norfentanyl and other inactive metabolites that do not contribute significantly to observed activity. Within 72 hours of administration, approximately 75% of an intravenous dose of fentanyl is excreted in the urine, with <10% representing unchanged drug.

The pharmacokinetic properties of intravenous fentanyl do not appear to be significantly affected in patients with compensated cirrhosis or renal insufficiency;[35] however, the effects of hepatic and renal failure on the pharmacokinetics of transdermal fentanyl have not been fully investigated. Theoretically, renal and hepatic failure could affect skin permeability, regional blood flow, protein binding and the clearance of fentanyl administered by the transdermal route.[36] Transdermal fentanyl should be used with caution in such patients and dosage should be decreased in patients who develop opioid-related adverse effects.

Average skin thickness throughout the body, except for certain areas such as the palms and soles, is 40μm and ranges between 20 and 80μm as a function of age, gender and race.[15] Fentanyl blood levels can increase by approximately 50% in patients with thinner skin (20μm) and decrease by one-third in patients with thicker skin (80μm). If a patch is applied to broken skin, fentanyl blood levels can increase to five times normal values.[15]

1.3 Effects of Age, Weight and Sex

Age does not appear to have a large impact on the absorption kinetics of transdermal fentanyl. Two small studies have shown that age has no significant effect on peak/steady-state fentanyl blood levels or the time required to achieve peak levels.[27,37] These reports suggest that elderly patients take 3–4 hours longer to achieve peak fentanyl blood levels compared with younger patients; however, the difference was not significant. In one study, the elimination half-life following removal of the transdermal system was significantly ($p < 0.05$) greater in the elderly (43.1 hours) compared with younger patients (20 hours).[27]

The safety of transdermal fentanyl has not been established in children and therefore its use is not recommended for patients under the age of 12 years or patients under the age of 18 years who weigh <50kg (110 lbs); however, exceptions have been made in young cancer patients. A small open-label study on 13 opioid-tolerant paediatric cancer patients treated with transdermal fentanyl described favourable outcomes with pharmacokinetic parameter estimates similar to those for adults.[38] Weight and sex are not known to have a large influence on fentanyl pharmacokinetics;[6,24,39] however, no studies have directly investigated the effects of these variables in patients treated with transdermal fentanyl. Fentanyl pharmacokinetics may be altered in elderly, cachectic and debilitated patients as a result of poor fat stores, muscle wasting and decreased fentanyl clearance.

2. Clinical Aspects

2.1 Chronic Cancer Pain

The efficacy and tolerability of transdermal fentanyl for the long-term treatment of cancer pain has been well documented in numerous studies.[9,10,14,40-46] Although the WHO recommends oral morphine as the standard pharmacological treatment for moderate to severe cancer pain, one study reported that 67% of patients with advanced cancer require two or more routes of administration during the last 4 weeks of life.[47] Transdermal fentanyl is often administered to advanced cancer patients with poor venous access or to patients who are unable to tolerate oral medications as a result of gastrointestinal problems such as nausea, vomiting, dysphagia, malabsorption or bowel obstruction. In addition, patients who experience inadequate pain relief or unmanageable adverse effects are often switched from one opioid to another in an attempt to identify a more favourable analgesic.[48-51] In these circumstances, transdermal fentanyl may provide more effective pain relief. Terminal cancer patients may require parenteral opioids and frequent dosage adjustments during the final few days of life due to fluctuating analgesic needs and/or the development of adverse effects. In these situations, transdermal fentanyl may not be an optimal treatment for end-stage cancer pain.

As new evidence supporting the efficacy of opioid substitution becomes available, the use of transdermal fentanyl for the treatment of cancer pain is likely to increase. Several clinical trials suggest that transdermal fentanyl causes less nausea, vomiting and constipation compared with other opioids.[2,9,10,25,41,43,52,53] The European Association for Palliative Care recently recommended transdermal fentanyl as an effective alternative to oral morphine in patients whose opioid requirements are stable.[54] These reports may prompt some physicians to use transdermal fentanyl as a first-line opioid for the treatment of cancer-related pain.

It is recommended that cancer patients be titrated to stable pain relief with short-acting oral or parenteral opioids prior to the initiation of transdermal fentanyl. Several reports describe the intravenous administration of fentanyl by continuous infusion and/or patient-controlled analgesia as effective methods for dose-finding in cancer patients.[9,10,14,55,56] Patients were then successfully converted from intravenous to transdermal fentanyl using a 1 **:** 1 (intravenous **:** transdermal) conversion ratio. Despite these recommendations, an open-label trial recently the documented the safe and effective use of transdermal fentanyl as a treatment for cancer pain in opioid-naive patients and another group of patients receiving only codeine.[57] Opioid-naive (n = 14) and codeine-using (n = 14) patients initiated therapy with transdermal fentanyl patches at a dosage of 25 μg/hour; immediate-release oral morphine was used as a rescue medication. Five of the patients remained on 25 μg/hour while the other patients were switched to higher dosages. A majority (68%) of the patients achieved good to excellent pain relief. No cases of clinically relevant respiratory depression were observed. Common opioid-related adverse effects were seen, and constipation was reported by 3 (11%) of the patients. Moreover, >20% of 1005 patients included in a national survey on cancer pain were either opioid-naive or had only received analgesics when required before initiation of transdermal fentanyl.[58] However, the authors of the survey emphasised that the use of transdermal fentanyl in opioid-naive patients is inconsistent with the recommendations of the WHO and suggest that only experienced pain specialists should consider such a practice and should use the lowest dosage available (25 μg/hour).

A randomised open-label crossover study on 202 cancer patients showed that 54% preferred treatment with transdermal fentanyl compared with 36% who preferred sustained-release morphine ($p = 0.037$).[2] At the end of the trial, significantly more patients found transdermal fentanyl to be more convenient than morphine tablets and also reported less interruption in the daily activities of themselves and their caregivers. Patients treated with transdermal fentanyl reported less constipation ($p < 0.001$) and daytime drowsiness ($p = 0.015$) but also reported greater sleep disturbance ($p = 0.004$) and shorter sleep dura-

tion ($p = 0.008$). A comparison between the two groups showed no significant differences in analgesia, vomiting, dyspnoea, appetite loss or diarrhoea.

The results of a large cross-sectional study ($n = 504$) showed that advanced cancer patients treated with transdermal fentanyl were more satisfied overall with their pain medication compared with those who received sustained-release oral morphine ($p = 0.035$).[3] The patients treated with transdermal fentanyl also experienced a significantly lower frequency ($p < 0.002$) and impact ($p < 0.001$) of opioid-related adverse effects. Measures of pain intensity, sleep adequacy and physical symptoms demonstrated no significant difference between treatment groups. These results were despite the fact that patients who received transdermal fentanyl were significantly older ($p < 0.001$) and had significantly lower functioning and well-being scores ($p = 0.001$).

Wong et al. performed a randomised open-label study in which 40 patients were initially treated with immediate-release morphine during a stabilisation phase and then switched to either transdermal fentanyl or sustained-release morphine.[59] There were no significant differences in analgesic efficacy or the development of adverse effects between the two study groups. In both groups, insomnia improved to a significant degree during therapy. There was a significant reduction in nausea and vomiting noted in the group treated with transdermal fentanyl.

A national survey conducted in Germany on 1005 patients treated with transdermal fentanyl, mostly for cancer pain, documented safe and effective use of the drug.[58] The percentage of patients who reported severe pain decreased from 50% on day 1 to 14% on day 3, with 42% of the patients continuing transdermal fentanyl until death. A majority of these patients receiving transdermal fentanyl were satisfied with their treatment. Only 5% of patients discontinued transdermal fentanyl because of adverse effects. A retrospective analysis of 64 cancer patients switched from other opioids to transdermal fentanyl documented improved pain relief or fewer adverse effects in 50% of those studied.[60]

2.2 Chronic Non-Malignant Pain

The long-term treatment of non-malignant pain with opioids has traditionally been rejected in the US due to the perceived fears of addiction, toxicity and tolerance.[4,61] As a result, the use of opioids for the treatment of chronic non-malignant pain remains less well established than for cancer pain.[62,63] Although several studies have shown that opioids can reduce non-malignant pain, the use of these drugs for such purposes continues to be heavily debated.[4,11-13,64-68] Opioid analgesics have recently become advocated by some medical professionals for the treatment of refractory non-malignant pain.[4,69] The limited available literature suggests that certain patients with chronic non-malignant pain can achieve meaningful analgesia using opioid therapy without the development of unmanageable adverse effects or aberrant drug-related behaviours.[4,66,70] Survey data suggest that the illicit use and/or diversion of prescription drugs appears to be uncommon in patients taking opioids for chronic non-malignant pain.[66,71] Barkin et al. reported that fewer than 1% of patients without a history of drug abuse develop addictive behaviour when treated with opioids in medical settings.[72]

Data on the use of transdermal fentanyl for the treatment of chronic non-malignant pain are still scarce. One open-label study included 50 patients with lower back pain that could not be adequately controlled with oral opioids.[11] These patients were switched to a dosage of transdermal fentanyl that corresponded to their current use of oral opioids. The dosage of transdermal fentanyl was then titrated over the course of 9–12 days based on the supplemental use of oral opioids according to the manufacturer's instructions, although 80% of patients remained on a transdermal fentanyl dosage of 25 μg/hour. Each patient was maintained on transdermal fentanyl for a 1-month period. At the end of the study, 86% of the patients experienced 'overall benefit' from transdermal fentanyl as a treatment for their lower back pain. Significant improvements in pain relief ($p < 0.0001$) and disability ($p = 0.016$) were identified with the use of transdermal fentanyl compared with oral opioids. Overall, there was no

significant improvement in the quality of sleep as assessed with the Verran Snyder-Halpern scale. However, subscale analysis showed that the number of night awakenings was significantly reduced ($p < 0.014$). The incidence of nausea and other mild adverse effects, including constipation, local skin reaction, lightheadedness or dizziness, sleepiness and agitation, was comparable to that reported in other studies on the use of oral opioids for chronic non-malignant pain.[61]

Dellemijn et al. conducted a 12-week open-label prospective study on 48 patients with various non-malignant neuropathic pain syndromes to assess the efficacy of prolonged transdermal fentanyl therapy.[12] Eighteen patients (37.5%) withdrew from the study prematurely because of insufficient pain relief, adverse effects, or both. Nausea was the most common adverse effect and was reported by more than 80% of patients. Constipation was reported by 36% of patients. No serious adverse events such as respiratory depression were observed. Seventeen (35%) of the 48 patients reported satisfactory pain relief with acceptable adverse effects. Thirteen patients decided to continue transdermal fentanyl after completion of the study and eight patients were still experiencing satisfactory pain relief 2 years later.

A randomised cross-over study (2×4 weeks) of 256 patients with various chronic non-malignant pain syndromes was recently performed to compare the efficacy and safety of transdermal fentanyl with sustained-release morphine.[13] A total of 196 patients completed the study. Average pain intensity was significantly lower with transdermal fentanyl compared with sustained-release morphine ($p < 0.001$), and 35% of patients reported adequate pain control with transdermal fentanyl compared with 23% of patients using sustained-release morphine ($p = 0.002$). Similarly, patients receiving transdermal fentanyl reported that pain had less of an impact on their behaviour, mood and activities of daily living during treatment ($p < 0.05$). A higher proportion of patients preferred transdermal fentanyl to sustained-release morphine (65% vs 28%), whereas 7% of patients expressed no preference. The main reason for such a preference was better pain control, followed by greater convenience and fewer adverse effects. Patients had higher overall quality-of-life scores during treatment with transdermal fentanyl. Constipation was experienced by 29% of patients at the end of the transdermal fentanyl treatment period compared with 48% of patients at the end of the sustained-release morphine treatment period ($p < 0.001$), whereas nausea was more common with transdermal fentanyl than with morphine (26% vs 18%). A higher number of patients withdrew from the study due to adverse events experienced during the transdermal fentanyl treatment period (10%) compared with the sustained-release morphine treatment period (5%).

A multicentre open-label trial was performed to assess the efficacy and safety of transdermal fentanyl in 532 patients with pain of non-malignant origin,[73] of whom 301 (57%) completed the trial and 231 (43%) discontinued the treatment prematurely. Of the patients who completed the study, 86% preferred transdermal fentanyl to their previous opioid treatment ($p < 0.01$). The most frequent treatment-related adverse events were nausea (31%), constipation (19%), and somnolence (18%). Respiratory depression occurred in <1% of patients. Bodily pain ratings improved from baseline on the Short Form 36 questionnaire.

Despite the encouraging results of these studies, the administration of transdermal fentanyl for the treatment of non-malignant pain still remains controversial. Large well-controlled trials are needed to establish guidelines for the administration of opioids to patients with chronic non-malignant pain.

2.3 Acute and Postoperative Pain

Although most of the initial clinical experience with transdermal fentanyl was obtained in the postoperative setting,[18,23-25,32] the product is now contraindicated for the treatment of acute and postoperative pain. The risk of life-threatening hypoventilation outweighs the therapeutic benefits of transdermal fentanyl in these populations of patients. Medical professionals should not be misled by numerous clinical trials performed in the past to

evaluate the use of transdermal fentanyl in postoperative patients.

The delayed pharmacokinetics and variable interpatient responses associated with the use of transdermal fentanyl make accurate dose-finding extremely difficult in patients with acute and postoperative pain. Since acute and postoperative pain tends to fluctuate and may improve rapidly, there is no opportunity for accurate dosage titration with the transdermal preparation. Patients with acute and postoperative pain are often over- or under-dosed since it is difficult to predict their transdermal fentanyl dosage requirements without an adequate titration period. Additionally, most patients with acute and postoperative pain are opioid-naive and, therefore, at higher risk for developing serious adverse effects with the use of a long-acting opioid preparation associated with delayed pharmacokinetics. Dangerously high serum fentanyl levels can occur in such circumstances, especially if surgery is cancelled or only mild pain is experienced. For these reasons, the use of transdermal fentanyl for the treatment of postoperative patients has been associated with a high incidence of adverse effects and hypoventilation.

In a controlled study involving 120 postoperative patients treated with transdermal fentanyl, nine patients were withdrawn due to the development of severe respiratory depression.[74] Another controlled study in the postoperative population was discontinued when 33% of the patients treated with transdermal fentanyl developed respiratory rates of <10 breaths/minute.[75] The US FDA reported a 4% incidence of respiratory depression when transdermal fentanyl was used for postoperative pain.[76] In addition, there have been several deaths attributed to the use of transdermal fentanyl in the postoperative setting.[77,78]

Although the use of transdermal fentanyl is recommended only for the treatment of chronic stable pain states, a recent report on 74 consecutive patients treated with transdermal fentanyl for acute pain due to mucositis from high-dose chemotherapy and autologous stem-cell transplantation described sufficient analgesia without the development of any severe adverse effects.[79] In addition, a prospective cross-over study assessed the antiemetic activity of transdermal fentanyl compared with standard emetic treatment in cancer patients receiving high-dose cisplatin.[80] Despite the fact that these patients did not have pain, treatment with transdermal fentanyl at a dosage of 75 μg/hour was well tolerated and no significant adverse effects were reported.

2.4 Guidelines for Use

Transdermal fentanyl is indicated only for patients who require continuous opioid administration for the treatment of chronic pain that cannot be managed with other medications such as short-acting opioids on an as-needed basis or non-opioid analgesics. Pain should be under relatively stable control prior to the initiation of transdermal fentanyl, since meaningful pain relief is not obtained until 12–16 hours after application. Transdermal fentanyl is not recommended for the treatment of postoperative pain, acute pain or uncontrolled chronic pain. In these circumstances, pain may decrease more rapidly than fentanyl blood levels can be adjusted with the use of transdermal fentanyl, which can lead to the development of serious adverse effects such as hypoventilation.[17] Clinicians who prescribe transdermal fentanyl should be familiar with the detection and management of hypoventilation, including the use of opioid antagonists.[17] Patients and their relatives must also be educated to recognise serious opioid-related adverse effects associated with transdermal fentanyl and should be instructed to immediately remove all transdermal fentanyl patches and seek medical attention if any of these symptoms develop.

Titration with short-acting oral or parenteral opioids is generally recommended prior to the initiation of transdermal fentanyl patches in order to ensure timely analgesia and prevent serious adverse effects.[31] Patients can then be switched to transdermal fentanyl after stable analgesia has been achieved. Initial dose-finding with transdermal fentanyl has been shown to result in a longer titration interval and a greater risk of adverse effects.[81] However, several recent publications have docu-

mented the safe and effective use of transdermal fentanyl for the treatment of cancer pain in opioid-naive patients.[57,58] The initial dosage of transdermal fentanyl should never exceed 25 μg/hour in an opioid-naive patient started on therapy without proper dose-finding using short-acting opioids.

Transdermal fentanyl 50, 75 and 100 μg/hour should only be used in opioid-tolerant patients already taking >135 mg/day of oral morphine or the equianalgesic dose of another opioid. Multiple transdermal patches may be used concomitantly to attain delivery rates higher than 100 μg/hour. The maximum number of patches that can be applied is determined by the area of suitable skin available.[82] Patches may be applied at multiple different locations throughout the upper torso in order to achieve the necessary dosage. No true ceiling effect exists for fentanyl administered by the transdermal route, and reports of patients receiving transdermal fentanyl dosages as high as 1000 μg/hour or greater are available.[41] Nonetheless, at our institution, we usually administer transdermal fentanyl at a dosage no higher than 500 μg/hour (100 μg/hour patches × 5). The main reason for such practice is that higher dosages require a larger skin application area, which tends to become burdensome for patients. Conversion to another form of long-acting opioid therapy may be considered when very high dosages of transdermal fentanyl are required for adequate pain relief.[41]

Residual fentanyl remains within the patch reservoir after 72 hours; however, the concentration gradient is too low to maintain adequate diffusion into the skin.[83] For this reason, it is recommended that transdermal fentanyl patches be replaced every 72 hours. Some patients may experience end-of-dose failure earlier than 72 hours after patch application. In such cases, an increase in transdermal fentanyl dosage is suggested; however, certain patients will require patch replacement every 48 hours. A recent study on 51 patients showed that application intervals needed to be shortened in 12 patients (23.5%) during long-term treatment with transdermal fentanyl.[41] Patches were changed on a 60-hour schedule in six patients; however, three of these patients eventually required changes every 48 hours. The other six patients were switched straight to a 48-hour cycle. Patch changes every 60 hours appeared to be unnecessary and uncomfortable for patients. This practice would require patch replacement every 2.5 days, one in the morning and the next in the evening. In cases where analgesia was not maintained for 72 hours, the authors recommend patch changes every 48 hours. Patches should not be replaced more frequently than every 48 hours, as 24-hour renewals have been reported to cause increased fentanyl blood levels and complications.[24]

When switching patients from oral or parenteral morphine to transdermal fentanyl, clinicians should follow these steps: (i) calculate the patient's 24-hour oral morphine requirement using the published equianalgesic table (table II); and (ii) determine the corresponding transdermal dosage according to the manufacturer's recommendations (table III). Clinicians must take care to ensure that a morphine dose expressed as mg/day is converted to a trans-

Table II. Equianalgesic potency conversion table.[17] All IM and PO doses in this chart are considered equivalent in analgesic effect to IM morphine 10mg

Drug	Equianalgesic dose (mg)	
	IM[a,b]	PO
Morphine	10	60 (30)[c]
Hydromorphone	1.5	7.5
Methadone	10	20
Oxycodone	15	30
Levorphanol	2	4
Oxymorphone	1	10 (PR)
Diamorphine (heroin)	5	60
Pethidine (meperidine)	75	
Codeine	130	200

a Based on single-dose studies in which an IM dose of each drug was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.[84]

b Although controlled studies are not available, in clinical practice it is customary to consider doses of opioid given IM, IV or SC to be equivalent. There may be some differences in pharmacokinetic parameters.

c The conversion ratio of parenteral morphine 10mg = oral morphine 30mg is based on clinical experience in patients with chronic pain. The conversion ratio of parenteral morphine 10mg = oral morphine 60mg is based on a potency study in acute pain.[85]

IM = intramuscular; **PO** = oral; **PR** = rectal; **SC** = subcutaneous.

dermal fentanyl dose expressed as μg/hour. Patients should continue a short-acting opioid analgesic on an as-needed basis during the initiation of transdermal fentanyl since therapeutic fentanyl blood levels will not be achieved for approximately 12–16 hours. Thereafter, patients may periodically require supplemental doses of short-acting opioids for the treatment of breakthrough pain.

The conversion from other opioids to transdermal fentanyl has been investigated less thoroughly and should therefore be performed with caution in order to prevent exacerbations of pain and/or opioid-related adverse effects. The general recommendation is to determine the patient's 24-hour opioid requirement and then calculate the equianalgesic dosage of oral morphine using the published conversion table (table II). The starting dosage of transdermal fentanyl can then be determined based on the 24-hour oral morphine requirement using the manufacturer's recommendations (table III).

Clinicians should be aware that the conversion tables are based on single-dose studies in which low doses of each drug were compared with morphine in order to determine the relative potency. These conversion tables were only intended for single-dose opioid administration and none have been established for use in long-term opioid therapy. Recent studies suggest that the published conversion tables underestimate the potency of opioids when administered on a long-term basis.[86,87] Moreover, the manufacturer's recommendations (table III) are conservative and only intended for converting patients from oral morphine to transdermal fentanyl. These recommendations should not be used in a reciprocal fashion to convert from transdermal fentanyl to other opioids, as this practice could result in overdosage and serious adverse effects.

Some patients may need to be switched from sustained-release preparations of oral morphine and oxycodone to transdermal fentanyl. In such cases, initial application of transdermal fentanyl should coincide with the patient's final dose of sustained-release oral opioid, since 12–16 hours are required to achieve therapeutic fentanyl blood levels. Short-acting oral or parenteral opioids (or non-opioid analgesics) should remain readily available as a rescue medication during the transition period.

The use of intravenous fentanyl administered by continuous infusion, patient-controlled analgesia or a combination of the two has also been described as an effective method for estimating hourly requirement for transdermal fentanyl.[9,10,14,55,56] Patients experiencing acute exacerbations of chronic cancer pain or those who are unable to take oral medications may benefit from these titration methods. Patients in these studies were switched from intravenous to transdermal fentanyl using a 1 : 1 (intravenous : transdermal) conversion ratio following titration to adequate pain relief with intravenous fentanyl. A recent prospective case series on 15 consecutive cancer patients describes the use of a 1 : 1 (intravenous : transdermal) conversion ratio and a two-step taper of the intravenous fentanyl infusion over 12 hours in order to account for the delayed therapeutic effects of transdermal fentanyl.[55] The use of intravenous fentanyl may also reduce the time required for titration and eliminate any discrepancies that could arise from incomplete

Table III. Recommended initial transdermal fentanyl dose based upon daily oral morphine dose.[17] In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to transdermal fentanyl[a]

24-hour oral morphine requirement (mg/day)	Transdermal fentanyl dose (μg/h)
45–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

a This table should not be used to convert from transdermal fentanyl to other therapies, since this conversion to transdermal fentanyl is conservative. Use of this table for conversion to other analgesic therapies can overestimate the dose of the new analgesic agent and result in overdosage.

cross-tolerance if another opioid were used for transdermal fentanyl dose-finding.

The delayed effects of transdermal fentanyl make dose titration more difficult during exacerbations of chronic pain. Another recent prospective case series documents nine consecutive cancer patients who were switched from transdermal to intravenous fentanyl in a safe and effective manner using a 1 : 1 (transdermal : intravenous) conversion during chronic pain crises.[88] In each of these nine patients, all transdermal patches were removed and a continuous infusion delivering intravenous fentanyl at the same rate was started simultaneously. Patients were also able to self-administer supplemental demand boluses of intravenous fentanyl using patient-controlled analgesia. Eight of these nine patients were later switched back to transdermal fentanyl once adequate analgesia was achieved using a 1 : 1 (intravenous : transdermal) conversion and 2-step taper of the intravenous fentanyl infusion.[55]

Transdermal fentanyl patches should be applied to a dry, non-irritated, non-hairy, non-irradiated flat area of the skin such as the upper arm, chest or flank. Patients may not become aware of a partially or completely dislodged patch applied to the back. We recommend pressing each patch in place for 30 seconds using the palm to provide adequate application. Care should be taken to ensure that all edges of the patch are well applied to the skin. When necessary, hair at the application site should be clipped rather than shaved in order to avoid skin abrasions that can result in a higher risk of local effects and systemic fentanyl absorption. Only water should be used to cleanse the skin area prior to patch application since soap, alcohol and other solvents may irritate the skin or alter its permeability. Transdermal fentanyl patches will not work properly and may be unsafe to use if cut or damaged. An excessive amount of fentanyl may be released too rapidly into the body if the rate-controlling membrane is not completely intact.

Patients can bathe, shower and swim while wearing transdermal fentanyl patches. If one or more patches fall off during exposure to water, all patches should be removed and replaced once the skin is dry. Patches can be secured with adhesive tape if necessary. If a patch dislodges from a patient and accidentally adheres to the skin of another individual, it should be immediately removed from that person and a physician should be consulted. Patients should be instructed to avoid exposure to external heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs and heated waterbeds while wearing transdermal fentanyl patches since elevated temperatures result in increased fentanyl release.[17] Application sites should be rotated in order to decrease variations in fentanyl blood levels that may result from the accumulation of subcutaneous skin depots.[31]

All patches should be simultaneously discarded and replaced any time the dosage of transdermal fentanyl is increased. For example, if the dosage is being increased from 100 to 125 μg/hour, the 100μg patch should be removed from the skin and new 100 μg/hour and 25 μg/hour patches should be applied. This method ensures that all transdermal patches will remain on the same replacement schedule in the future.

The concomitant use of short-acting oral or parenteral opioids on an as-needed basis helps patients maintain adequate pain relief during the initiation and subsequent titration of transdermal fentanyl. Patients should be told that they may temporarily require rescue medications as frequently as every 3–4 hours during the initiation of transdermal fentanyl therapy. Following the conversion to transdermal fentanyl, patients should be monitored carefully and further titrated if necessary on the basis of pain relief, adverse effects and supplemental opioid use.

Some pain experts criticise the manufacturer's recommendations (table III) for switching patients from oral morphine to transdermal fentanyl as being too conservative. These clinicians warn that the initial dosages of transdermal fentanyl calculated using this conversion chart are inadequate and will result in the undertreatment of many patients.[83] Studies based on the manufacturer's conversion chart have reported the need for frequent dosage increases following conversion to transdermal fenta-

nyl.[2] Several trials have reported that the manufacturer's recommended starting dosages are too low for approximately 50% of cancer patients switched from other opioids to transdermal fentanyl.[8,22,45] Nevertheless, the manufacturer's recommendations appear to provide a convenient, well-tolerated starting dosage of transdermal fentanyl for many patients provided that short-acting rescue medications are readily available until adequate titration is achieved [52,89] Short-acting opioid or non-opioid rescue medications should continue to be used for episodes of breakthrough pain after an optimal dosage of transdermal fentanyl is identified. The use of short-acting opioid rescue medications such as immediate-release morphine, oxycodone and hydromorphone may help to prevent opioid accumulation and toxicity in the setting of background fentanyl blood levels.[89] Many clinicians prescribe a dosage of rescue medication equivalent to 10% of the total 24-hour fentanyl requirement.

Recently, a less conservative alternative dosage algorithm for opioid-tolerant cancer patients has been suggested based on the extensive clinical experience of several pain specialists.[83] Using this conversion ratio of 100 **:** 1 (oral morphine **:** transdermal fentanyl), oral morphine 60 mg/day is equivalent to transdermal fentanyl 0.6 mg/24 hours (25 μg/hour). This 100 **:** 1 ratio is still viewed by some as being too conservative, but is closer to the 70 **:** 1 equianalgesic ratio supported by another study.[90]

Additionally, the authors of a retrospective analysis of 64 cancer patients switched from other opioids to transdermal fentanyl proposed a conversion rate between 70 **:** 1 and 100 **:** 1 (slow-release morphine **:** transdermal fentanyl).[60] The authors proposed a conversion ratio between 70 **:** 1 and 100 **:** 1 when switching from slow-release morphine to transdermal fentanyl.

Evaluation of the analgesic efficacy of transdermal fentanyl cannot be made for at least 24 hours following initial patch application since fentanyl blood levels continue to rise during this period. If adequate analgesia is not achieved after 72 hours, the initial transdermal fentanyl dosage may be increased based on the supplemental use of short-acting oral opioids during the second or third days following patch application (table IV). The manufacturer suggests that supplementary use of 90mg of oral morphine over 24 hours is equivalent to a 25 μg/hour increase in transdermal fentanyl. Thereafter, we recommend that patients wear the higher dosage for at least 3 days before any further adjustments are made. Titration on a day-to-day basis makes no pharmacokinetic sense because it takes longer than 24 hours to reach maximal fentanyl blood levels and approximately 72 hours to reach steady-state blood levels in most patients.[30,91] Patients who are taken off transdermal fentanyl therapy for non-emergency reasons should be gradually tapered off the drug or switched to an alternative opioid preparation in order to prevent withdrawal symptoms. We recommend tapering patients off transdermal fentanyl in 25μg increments every 72 hours. Once all patches have been removed, patients can use a short tapering schedule of a short-acting opioid in order to prevent any withdrawal symptoms. The exact dosage at which transdermal fentanyl therapy can be discontinued without producing signs and symptoms of withdrawal is not known.

Used patches should all be removed, folded in half so that the adhesive layer sticks to itself, and immediately flushed down the toilet prior to their replacement. Used patches may contain enough residual fentanyl (28–84.4% of starting dose) to cause serious toxicity in children, opioid-naive adults and pets.[83,92] Unused patches that are left over from a prescription should be disposed in a similar manner or returned to the pharmacy for disposal. The pouch and protective liner should not be flushed. Patches should remain in their protective

Table IV. Recommended dosage increases in transdermal fentanyl based on supplemental breakthrough medication use[17]

Oral opioid	Breakthrough medication used (mg/day)	Recommended increase in dosage of transdermal fentanyl
Codeine	300	Add 25 μg/h (add patch or change to higher dosage patch)
Oxycodone	45	
Hydromorphone	12	
Morphine	90	

pouches away from the reach of children and pets until needed for use.

Patients may experience cognitive and physical impairments such as confusion and abnormal coordination with the use of transdermal fentanyl. Therefore, it is recommended that patients refrain from driving or operating machinery following the initiation of transdermal fentanyl or after any increase in dosage of the drug. Patients may resume such activities once the absence of these potential adverse effects with transdermal fentanyl is documented.

2.5 Benefits

The numerous benefits associated with transdermal fentanyl have been discussed throughout the course of this manuscript. Administration of transdermal fentanyl provides continuous controlled systemic delivery of the potent opioid fentanyl for 72 hours in a non-invasive manner. Transdermal fentanyl patches offer an attractive analgesic alternative for cancer patients, especially those who are unable to swallow or have gastrointestinal problems as a result of their malignancy, such as nausea, vomiting or bowel obstruction. Several studies have also shown that transdermal fentanyl can be used as a well tolerated and effective treatment for chronic non-malignant pain.[11-13] In addition, the parenteral formulation of fentanyl can be administered intravenously to titrate patients to adequate pain relief prior to the initiation of transdermal fentanyl.

Patients have demonstrated a lower incidence and impact of adverse effects, a higher degree of satisfaction, better quality of life, improved compliance, decreased use of rescue medication and less perceived guilt and/or shame regarding the need to use opioids during treatment with transdermal fentanyl compared with oral morphine.[2,3,8,89,93,94] Lower incidences of constipation,[2,9,10,25,41,43,53] laxative use,[95] nausea and vomiting,[9,10,52,53] disrupted sleep[45] and daytime drowsiness[2] have been described in many studies comparing transdermal fentanyl with other oral opioids. The adminstration of opioids can cause systemic histamine release and result in adverse effects such as pruritus. Histamine assays and skin wheal testing in humans indicate that clinically significant histamine release rarely occurs with fentanyl administration and was not shown to occur at dosages as high as 50 μg/hour.[17]

3. Adverse Effects

3.1 Respiratory

Hypoventilation is the most serious adverse effect associated with opioid therapy. Morphine and fentanyl produce similar degrees of hypoventilation at equivalent analgesic blood levels; however, the delayed pharmacokinetic properties associated with the use of transdermal fentanyl may result in prolonged respiratory compromise that requires sequential doses or a continuous infusion of an opioid antagonist.[18,28,30] Hypoventilation associated with the use of transdermal fentanyl has been shown to occur more frequently in the setting of acute and postoperative pain, and use of the drug is now contraindicated for such purposes.[74-78] Transdermal fentanyl should be administered cautiously to patients with pre-existing medical conditions such as emphysema that may predispose them to the development of hypoventilation, since normal analgesic doses of opioids may lead to respiratory failure. Numerous reports of serious respiratory effects related to transdermal fentanyl have been described in the literature and are well summarised in a review by Grond et al.[36]

Although the following reports are intended to remind readers that transdermal fentanyl can cause life-threatening toxicity, severe respiratory compromise is relatively uncommon when the drug is administered according to the manufacturer's suggested guidelines. A survey of 1005 patients treated with transdermal fentanyl for the management of cancer pain documented the development of dyspnoea in seven patients and apnoea in one other patient.[58] Two of these patients required artificial respiration and recovered without sequelae. A 77-year-old man developed postoperative respiratory failure following a radical nephrectomy after receiving epidural bupivacaine and diamorphine in addition to a 25 μg/

hour transdermal fentanyl patch that had been initiated 3 weeks earlier.[96]

Many reports of adverse respiratory effects associated with transdermal fentanyl involve inappropriate or illicit use of the drug.[97,98] A 17-year-old was found dead on a heated waterbed after being prescribed transdermal fentanyl for pain due to a wisdom tooth extraction.[78] Following an endoscopic procedure performed under general anaesthesia, a 42-year-old woman treated with transdermal fentanyl for cancer pain developed respiratory depression. A heating pad applied to her abdomen had slipped onto the fentanyl patch applied to her chest.[99] A 57-year-old woman with a 75 μg/hour transdermal fentanyl patch applied to her chest developed respiratory depression during repair of a tibial stress fracture when an upper-body warming blanket was placed intraoperatively.[100] A 44-year-old man was treated for approximately 1 year with transdermal fentanyl 75 μg/hour for HIV neuropathy. He became stuporous while engaging in outdoor activities in the summer heat.[101] The rise in his body temperature probably increased the systemic absorption of fentanyl. A 19-year-old woman treated with transdermal fentanyl 100 μg/hour for acute abdominal pain died at home from respiratory depression.[77] In another report, a transdermal patch was unintentionally transferred from the skin of a patient to the back of her 2-year-old grandson while she was hugging him in bed.[102] The child experienced respiratory depression that resolved following removal of the patch and the administration of naloxone. One 22-year-old man with neuropathic pain developed hypoventilation within 1 hour of applying one-fourth of a 50 μg/hour patch that had been cut into pieces.[103]

A 31-year-old funeral home employee died from fentanyl toxicity after removing a used patch from a deceased person.[104] However, the route that he used to self-administer the residual fentanyl was not known. Another 36-year-old man developed respiratory depression after heating and inhaling the contents from a fentanyl patch.[105] He collapsed immediately after one inhalation with a respiratory rate of 6 breaths/minute, a heart rate of 120 beats/minute and unobtainable blood pressure. He responded favourably to an injection of naloxone. Inhalation of fentanyl results in greater systemic absorption and high potential for overdose. One patient developed respiratory arrest after injecting the contents of her fentanyl patch into a central venous catheter.[106]

A 31-year-old man presented to the emergency department in respiratory arrest and died from fentanyl overdose.[107] During intubation, a transdermal fentanyl patch (75 μg/hour) was recovered from his buccal cavity and another patch (75 μg/hour) was found on his right thigh. Post-mortem blood evaluation revealed a venous fentanyl level of 17.2 μg/L. The therapeutic range of fentanyl for analgesic use is 1–3 μg/L. This patient's drug screen was also positive for benzodiazepines and cocaine. An 83-year-old woman with terminal cancer was found dead with three 100 μg/hour fentanyl patches on her chest.[108] Fentanyl overdose was determined to be the cause of death; however, it was never established whether this was an accidental overdose, suicide, assisted suicide or possible homicide.

3.2 Withdrawal Syndrome

Some patients have reported symptoms of acute withdrawal despite adequate analgesia when switched from sustained-release morphine to transdermal fentanyl.[2,109-111] Symptoms included abdominal pain, agitation, 'flu-like' symptoms and sweating. Although the precise mechanism responsible for withdrawal has not been clarified, the symptoms improved with short-acting morphine and have been attributed to physical rather than psychological dependence. Possible explanations for these withdrawal symptoms may include differences between the drugs in terms of μ receptor affinity/specificity, pharmacokinetics or distribution profiles at central and peripheral opioid receptors. A recent report also describes the development of myoclonus due to withdrawal from transdermal fentanyl.[112]

3.3 Other Risks

Many of the potential risks and adverse effects associated with transdermal fentanyl have been described throughout this manuscript. Table V illus-

Table V. Summary of the adverse events that occurred in more than 1% of cancer patients during the premarketing clinical trials with transdermal fentanyl (n = 153)[17]

System	Adverse event and incidence		
	1–2%	3–10%	>10%
Cardiovascular	Arrhythmia, chest pain		
Digestive	Flatulence	Anorexia, diarrhoea, dyspepsia, abdominal pain	Nausea, vomiting, constipation, dry mouth
Nervous	Tremor, abnormal co-ordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paraesthesia, amnesia, syncope, paranoid reaction	Dizziness, nervousness, hallucinations, anxiety, depression, euphoria, headache	Somnolence, confusion, asthenia
Respiratory	Haemoptysis, pharyngitis, hiccups, hypoventilation	Dyspnoea, apnoea	
Skin and appendages	Rash, application site reaction (erythema, papules, itching, oedema)	Pruritis	Sweating

trates the frequency of adverse events that occurred in more than 1% of 153 cancer patients during the premarketing clinical trials with transdermal fentanyl (dosage range 25–600 μg/hour).[17] Hypoventilation is the most serious complication associated with transdermal fentanyl and has been reported to occur in 2% of cancer patients treated with the drug.[76] Fentanyl and morphine produce similar degrees of hypoventilation at equivalent analgesic blood levels. The risk of hypoventilation associated with transdermal fentanyl increases in opioid-naive patients at fentanyl blood levels >2 μg/L, especially in patients with underlying pulmonary conditions or those who are receiving other drugs that can cause respiratory compromise. Fentanyl blood levels may be useful in certain clinical situations; however, they do not reflect patient sensitivity to the drug nor should they be used as a sole indicator of effectiveness or toxicity.

Numerous clinical studies have reported that transdermal fentanyl causes less constipation than oral morphine.[2,9,10,25,41,53] Despite these findings, transdermal fentanyl therapy can result in the development of constipation and an appropriate bowel regimen should be initiated when symptoms develop. The incidence of nausea and vomiting in patients treated with transdermal fentanyl was similar to that reported for morphine in some studies.[2,9,14] However, in other reports, transdermal fentanyl appeared to result in significantly lower rates of nausea and/or vomiting.[9,10,52,53]

The incidence and severity of anorexia, urinary disorders, sweating, dizziness and dry mouth in patients receiving transdermal fentanyl was either the same or non-significantly lower than in those treated with morphine.[9,81] Episodes of acute delirium have been reported in patients treated with transdermal fentanyl, but the symptoms eventually disappeared after the drug was discontinued and fentanyl blood levels decreased.[113,114] Fentanyl does not usually exert major effects on the cardiovascular system at therapeutic dosages; however, some patients may experience bradycardia, orthostatic hypotension and/or fainting.[17] For this reason, transdermal fentanyl should only be used with caution in patients with bradycardia.

Transdermal patches contain a relatively large quantity of fentanyl in order to maintain an adequate diffusion gradient across the skin (table I). Marquardt et al. analysed the remaining contents of nine transdermal patches and determined that 28–84.4% of the original fentanyl content still remained after 72 hours of continuous use.[92] The authors also demonstrated that these amounts of residual fentanyl were sufficient for significant abuse and could result in potentially lethal doses. They warned that adequate disposal policies have not been established and need to be implemented. Another report suggests that approximately 40% of fentanyl remains

following a 72-hour application of transdermal fentanyl.[83]

There have been several case reports of fentanyl overdose resulting from exposure to a heating pad or elevated body temperatures.[78,99-101] However, no previous studies have formally addressed the effects of heat on transdermal pharmacokinetics. Heat is expected to increase skin permeability and lead to accelerated metabolism and elimination of transdermal fentanyl.[36] An increase in body temperature of 3°C is expected to increase maximal fentanyl blood levels by 25%. Intracutaneous blood flow has a significant effect on systemic uptake of fentanyl from the cutaneous reservoir. An increase in skin temperature from 32°C to 40°C leads to a gradual increase in cutaneous blood flow to 10–15 times that of controls as measured by Doppler flowmetry.[115] Under normal conditions, intersubject variability in fentanyl absorption rate is probably only minimally affected by skin site temperature, since the temperature remains relatively consistent among subjects.[15]

A retrospective case series showed that nine out of 18 cases of adverse exposures to transdermal fentanyl required hospitalisation; however, all the cases were related to intentional abuse of the drug including excessive use, injection of fentanyl residue, chewing and/or swallowing the patches.[19] One of these nine patients died of anoxic encephalopathy following cardiac arrest. Another patient in this series became mildly intoxicated after cutting his fentanyl patch in half before application in order to decrease the dosage. As a result, fentanyl spread over a wider area of skin, causing increased systemic absorption.

The Drug Abuse Warning Network (DAWN) is a national surveillance system that gathers data on drug-related emergency visits.[116] This information focuses on drugs of abuse and is collected from a national probability sample of non-Federal short-stay hospital emergency departments. Cases that involve persons between the ages of 6 and 97 years and include evidence of intentional abuse or misuse of a drug (drug abuse, drug dependence, recreational use or suicide attempt) are reportable to DAWN. Adverse reactions related to proper use or accidental ingestion/inhalation of a drug are not reportable. Figure 2 illustrates the number of emergency department visits compiled by DAWN related to the intentional abuse or misuse of various opioids. Fentanyl-related visits increased significantly from 1994 to 2001; however, the overall number remained relatively small.

A summary of 21 uncontrolled trials revealed that skin irritation was observed in 8–20% of patients wearing transdermal fentanyl patches, but never resulted in withdrawal from a study.[36] Local erythema and itching has been attributed to an occlusive effect and irritation rather than contact dermatitis.[117]

Transdermal fentanyl is classified as pregnancy category C. In animal studies, fentanyl has been shown to impair fertility and to have embryocidal effects; however, no evidence of teratogenic effects has been observed. There are no well-controlled studies on the use of transdermal fentanyl in pregnant women. Therefore, transdermal fentanyl should be used during pregnancy only if the potential benefits heavily outweigh potential risks to the foetus. Transdermal fentanyl is not recommended for analgesia during labour and delivery. Fentanyl is excreted in human milk and is not recommended for use in nursing women because of possible adverse effects on their infants.[17]

Coadministration of transdermal fentanyl and other drugs that are metabolised by or inhibit the CYP3A4 isoenzyme may result in decreased fentanyl clearance rates.[34] Patients who require such drugs concomitantly with transdermal fentanyl should be monitored carefully and dosage adjustments should be made if warranted. Additionally, inducers of CYP3A4 can increase fentanyl clearance and may result in decreased effects of the drug.[34]

CNS depressants (such as other opioids, anticonvulsants, sedatives, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, antihistamines and alcoholic beverages) may produce additive depressant effects when administered concomitantly with transdermal fentanyl. In these circumstances, hypoventilation, hypotension and

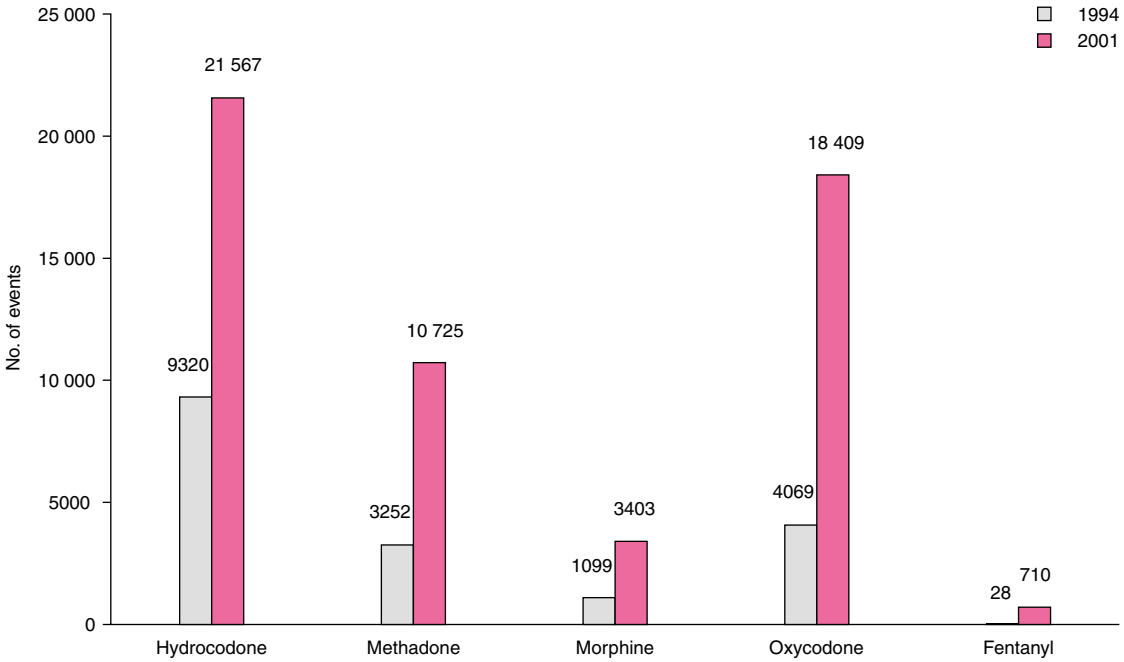

Fig. 2. Emergency department visits related to the intentional abuse or misuse of various opioids, 1994 and 2001. Data collected from a national probability sample of non-Federal short-stay hospital emergency departments by the Drug Abuse Warning Network surveillance system.[116]

profound sedation or coma may occur. Clinicians should consider reducing the dosage of transdermal fentanyl, the CNS depressant or both agents in order to prevent the development of adverse effects.

4. Economic Aspects

The growing armamentarium of analgesic therapies has generated greater interest in cost issues related to the administration of opioid medications.[118] Cost considerations include not only the price of pain medications themselves, but also the additional equipment, consumables and medical assistance required for administration. The costs associated with transdermal fentanyl therapy are probably highest during the titration phase when increased staffing and rescue medications are required. Comparisons of average wholesale price show that transdermal fentanyl is similar in cost to an equivalent dosage of sustained-release morphine (table VI); however, such estimates depend on the equianalgesic conversion ratio used and the sustained-release morphine preparation considered.

No head-to-head clinical trials comparing the costs of long-acting opioids have been performed to date. A recent cost-utility modelling analysis showed transdermal fentanyl to be more expensive than controlled-release morphine or controlled-release oxycodone for chronic moderate to severe pain in an outpatient setting.[119] Transdermal fentanyl had an estimated cost of $US2491 during the first year of therapy compared with $US2037 for controlled-release morphine and $US2307 for controlled-release oxycodone (1997 values). However, transdermal fentanyl was also associated with the highest expected number of quality-adjusted life days (QALDs): 244 compared with 236 for controlled-release morphine and 231 for controlled-release oxycodone. In this conservative analysis, transdermal fentanyl resulted in increased QALDs at a nominal increased cost. Further analysis will be

Table VI. Acquisition costs of long-term opioid therapy: comparison of average wholesale prices in the US in 2001[a]

Drug	Dose[b]	Schedule	AWP per dose ($US)	AWP per day ($US)[c]
Mild-to-moderate pain				
Short-acting oral preparations				
Codeine	60mg	q4h	0.80	4.80
Dextropropoxyphene	100mg	q4h	0.33	1.98
Hydrocodone (+ paracetamol [acetaminophen])	10mg	q4h	0.53	3.18
Oxycodone (+ aspirin/paracetamol)	10mg	q4h	0.52	3.12
Moderate-to-severe pain				
Short-acting oral preparations				
Oxycodone, immediate release	20mg	q4h	0.31	1.86
Morphine, immediate release	30mg	q4h	0.31	1.86
Hydromorphone	8mg	q4h	1.22	7.32
Levorphanol	4mg	q6h	0.87	3.48
Transmucosal preparations				
Oral transmucosal fentanyl citrate	200μg	q6h	6.95	27.80
	400μg	q6h	8.93	35.72
	600μg	q6h	10.91	43.64
	800μg	q6h	12.90	51.60
	1200μg	q6h	16.87	67.48
	1600μg	q6h	20.83	83.32
Long-acting oral preparations				
Oxycodone, controlled-release	60mg	q12h	6.60	13.20
Morphine, controlled-release (MS Contin®)[d]	90mg	q12h	5.58	11.16
Morphine, controlled-release (Kadian®)[d]	150mg	q24h	9.63	9.63
Methadone	5mg	q8h	0.09	0.27
Transdermal preparations				
Transdermal fentanyl	25 μg/h	q72h	12.33	4.11
	50 μg/h	q72h	20.37	6.79
	75 μg/h	q72h	32.63	10.88
	100 μg/h	q72h	40.65	13.55

a AWPs were averaged for all suppliers using the 2001 edition of RedBook™ for Windows version 4.0 (Medical Economics Data, Montvale, NJ, USA). Costs to patients are variable and approximately 10–20% above AWPs for outpatients and 50–200% above AWPs for inpatients. Costs to pharmacies are based on product volume discounts and can be considerably less than AWP.

b Doses are not intended to be equianalgesic.

c Mean AWP for available products multiplied by the number of doses required in a 24-hour period.

d Use of trade names is for product identification only and does not imply endorsement.

AWP = average wholesale price; **qxh** = every *x* hours.

required to assess the full economic benefits of transdermal fentanyl compared with other opioids.

Transdermal fentanyl accounted for a 23% market share of the long-acting opioids (outpatient, mail order and long-term care prescriptions) dispensed during the year 2000 in the US (figure 3).

5. Conclusions

Chronic pain can be treated using a novel transdermal delivery system that provides 72 hours of controlled systemic delivery of the potent opioid fentanyl. This non-invasive formulation is a valuable therapeutic alternative to other long-acting

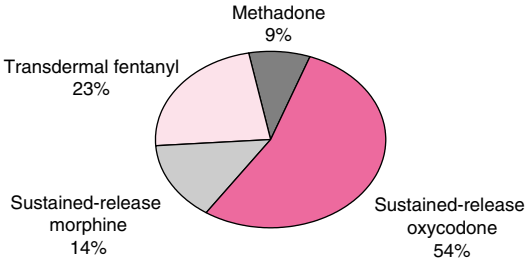

Fig. 3. Relative market share of long-acting opioid prescriptions dispensed during the year 2000 in the US, including outpatient, mail order and long-term care prescriptions. Data from IMS Health, National Prescription Audit Plus™.

opioid preparations, especially in cancer patients with compromised gastrointestinal function. In addition, patients who experience inadequate pain relief or unmanageable adverse effects are often switched from one opioid to another in an attempt to identify a more favourable analgesic. In these circumstances, transdermal fentanyl may be considered as an alternative opioid. The use of transdermal fentanyl for the treatment of chronic pain is likely to increase as additional evidence supporting the efficacy of opioid substitution becomes available. Some clinicians now prescribe transdermal fentanyl as their first-line long-acting opioid.

Patients have reported a higher degree of satisfaction, improved quality of life, better compliance, decreased use of rescue medication and less perceived guilt and/or shame regarding the need to use opioids with transdermal fentanyl compared with oral morphine. Lower incidences of constipation, laxative use, nausea and vomiting, disrupted sleep and daytime drowsiness have also been demonstrated in many studies comparing transdermal fentanyl with oral opioids. Transdermal fentanyl is contraindicated as a treatment for acute and postoperative pain, since these circumstances do not provide an opportunity for reliable dose finding and can lead to higher rates of opioid-related toxicity and hypoventilation.

Fentanyl blood levels increase slowly after patch application (12–16 hours to reach therapeutic levels) and decrease slowly after patch removal (half-life 16–22 hours). Patients should generally be titrated to adequate pain relief with short-acting oral or parenteral opioids prior to the initiation of transdermal fentanyl. This method helps accurate estimation of transdermal dosage requirements and also helps to prevent pain and adverse effects that can occur as a result of the delayed onset of action of transdermal fentanyl. Clinicians may consider using intravenous fentanyl as a means of estimating transdermal fentanyl requirements before therapy is initiated.

The pharmacokinetic delays associated with transdermal fentanyl can result in the development of prolonged life-threatening toxicity. Adverse effects should not be expected to diminish quickly following removal of transdermal fentanyl patches, and may take many hours to improve. Patients and their relatives must be instructed how to recognise symptoms of serious opioid-related toxicity such as hypoventilation and cognitive impairment. Any patient who develops these symptoms requires urgent medical evaluation following immediate removal of all transdermal fentanyl patches from the skin. Patients who experience hypoventilation should be immediately treated with an opioid antagonist and closely monitored for 24 hours. As a result of the depot effect associated with transdermal fentanyl, these individuals may require sequential doses or a continuous infusion of opioid antagonist. Transdermal fentanyl is a well tolerated and effective treatment for chronic pain. The benefits of transdermal fentanyl outweigh the potential risks when administered appropriately according to the correct guidelines summarised in this manuscript.

Acknowledgements

Craig Kornick, M.D., and Natalia Moryl, M.D., were sponsored by the National Cancer Institute's Psychiatry and Pain Research Training Grant (T32-CA09461), Department of Health and Human Services, Public Health Service. Juan Santiago-Palma, M.D., was sponsored in part by the Hale Matthews Foundation and a supportive care and rehabilitation fund of the Henry and Lucy Moses Foundation. We acknowledge Glenn Schulman, Pharm.D., in the Department of Pharmacy at Memorial Sloan-Kettering Cancer Center for his assistance in the construction of the average wholesale price table. We appreciate the assistance of Kristan Hahn in the preparation of the manuscript.

Richard Payne M.D. is a member of Janssen's Chronic Pain Scientific Advisory Board. Craig Kornick, M.D., Natalia Moryl, M.D. and Richard Payne M.D. have received honororia from Janssen Pharmaceutica for speaking engagements.

References

1. Woodroofe MA, Hays H. Fentanyl transdermal system: pain management at home. Can Fam Physician 1997; 43: 268-72
2. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. J Pain Symptom Manage 1997; 13: 254-61
3. Payne R, Mathias SD, Pasta DJ, et al. Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. J Clin Oncol 1998; 16: 1588-93
4. McCarber BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. Am J Ther 2001; 8: 181-6
5. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Molinoff PB, Ruddon RW, editors. Goodman and Gilman's the pharmacological basis of therapeutics. New York (NY): McGraw-Hill, 1996: 543-544
6. Bovill JG. Which potent opioid? Important criteria for selection. Drugs 1987; 33: 520-30
7. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. Clin Pharmacokinet 1983; 8 (5): 422-46
8. Simmonds MA, Payne R, Richenbacher J, et al. TTS fentanyl in the management of pain in patients with cancer [abstract]. Proc Am Soc Clin Oncol 1989; 8: 324
9. Zech D, Grond S, Lynch J, et al. Transdermal fentanyl and initial dose-finding with patient-controlled analgesia in cancer pain: a pilot study with 20 terminally ill cancer patients. Pain 1992; 50: 293-301
10. Grond S, Zech D, Lehmann K, et al. Transdermal fentanyl in the long-term treatment of cancer pain: a prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck region. Pain 1997; 69: 191-8
11. Simpson K, Edmonson EA, Constant CE, et al. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage 1997; 14: 218-24
12. Dellemijn PL, Van Duijn H, Vanneste JA. Prolonged treatment with transdermal fentanyl in neuropathic pain. J Pain Symptom Manage 1998; 16: 220-9
13. Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001; 322: 1154-8
14. Miser AW, Narang PK, Dothage JA, et al. Transdermal fentanyl for pain control in patients with cancer. Pain 1989; 37: 15-21
15. Gupta SK, Southam M, Gale R, et al. System functionality and physiochemical model of fentanyl transdermal system. J Pain Symptom Manage 1992; 7 (3 Suppl.): S17-26
16. Lehmann KA, Zech D. Transdermal fentanyl: clinical pharmacology. J Pain Symptom Manage 1992; 7: S8-16
17. Janssen Pharmaceutica. Duragesic® (fentanyl transdermal system) [package insert]. Titusville (NJ): Janssen Pharmaceutica Products, L.P., 2001
18. Varvel JR, Shafer SL, Hwang SS, et al. Absorption characteristics of transdermally administered fentanyl. Anesthesiology 1989; 70: 928-34
19. Roberge RJ, Krenzelok EP, Mrvos R. Transdermal drug delivery system exposure outcomes. J Emerg Med 2000; 18: 147-51
20. Roy SD, Flynn GL. Transdermal delivery of narcotic analgesics: pH, anatomical, and subject influences on cutaneous permeability of fentanyl and sufentanil. Pharm Res 1990; 7: 842-7
21. Rung GW, Riemondy S. The effect of skin temperature on transdermal fentanyl therapy [abstract]. Anesth Analg 1993; Suppl. 76: 363
22. Southam MA. Transdermal fentanyl therapy: system design, pharmacokinetics, and efficacy. Anticancer Drugs 1995; 6 Suppl. 3: 29-34
23. Holley FO, Van Steennis C. Postoperative analgesia with fentanyl: pharmacokinetics and pharmacodynamics of constant-rate IV and transdermal delivery. Br J Anaesth 1988; 60: 608-13
24. Gourlay GK, Kowalski SR, Plummer JL, et al. The transdermal administration of fentanyl in the treatment of postoperative pain: pharmacokinetics and pharmacodynamic effects. Pain 1989; 37: 193-202
25. Gourlay GK, Kowalski SR, Plummer JL, et al. The efficacy of transdermal fentanyl in the treatment of postoperative pain: a double-blind comparison of fentanyl and placebo systems. Pain 1990; 20: 21-8
26. Broome IJ, Wright BM, Bower S, et al. Postoperative analgesia with transdermal fentanyl following lower abdominal surgery. Anaesthesia 1995; 50: 300-3
27. Estéve M, Levron JC, Flaisler B, et al. Does aging modify pharmacokinetics of transdermal fentanyl? [abstract]. Anesthesiology 1991; 75 (3A): A705
28. Plezia PM, Kramer TH, Linford J, et al. Transdermal fentanyl: pharmacokinetics and preliminary clinical evaluation. Pharmacotherapy 1989; 9: 2-9
29. Van Bastelaere M, Rolly G, Van Peer A. Pharmacokinetic behavior of transdermal fentanyl [abstract]. Br J Anaesth 1993; 70 Suppl. 1: 75
30. Portenoy RK, Southam MA, Gupta SK, et al. Transdermal fentanyl for cancer pain: repeated dose pharmacokinetics. Anesthesiology 1993; 78: 36-43
31. Payne R. Transdermal fentanyl: suggested recommendations for clinical use. J Pain Symptom Manage 1992; 7: S40-4
32. Duthie DJR, Rowbotham DJ, Wyld R, et al. Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. Br J Anaesth 1988; 60: 614-8
33. Von Bormann B. Clinical experience. In: Lehmann KA, Zech D, editors. Transdermal fentanyl. Berlin: Springer, 1991: 119-40
34. Barkin RL, Barkin D. Pharmacologic management of acute and chronic pain: focus on drug interactions and patient-specific pharmacotherapeutic selection. South Med J 2001; 94: 756-70
35. Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl, and sufentanil: an update. Clin Pharmacokinet 1996; 31 (4): 275-92
36. Grond S, Radbruch L, Lehmann KA. Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. Clin Pharmacokinet 2000; 38 (1): 59-89
37. Thompson JP, Bower S, Liddle AM, et al. Perioperative pharmacokinetics of transdermal fentanyl in elderly and young adult patients. Br J Anaesth 1998; 81: 152-4
38. Collins JJ, Dunkel IJ, Gupta SK, et al. Transdermal fentanyl in children with cancer pain: feasibility, tolerability, and pharmacokinetic correlates. J Pediatr 1999; 134: 319-23
39. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987; 240: 159-66

40. Hammack JE, Mailliard JA, Loprinzi CL, et al. Transdermal fentanyl in the management of cancer pain in ambulatory patients: an open-label pilot study. Pain 1996; 12: 234-40
41. Donner B, Zenz M, Strumpf M, et al. Long-term treatment of cancer pain with transdermal fentanyl. J Pain Symptom Manage 1998; 15: 168-75
42. Herbst LH, Strause LG. Transdermal fentanyl use in home-care patients with chronic cancer pain. J Pain Symptom Manage 1992; 7 Suppl. 3: S54-7
43. Slover R. Transdermal fentanyl: clinical trial at the University of Colorado Health Sciences Center. J Pain Symptom Manage 1992; 7 Suppl. 3: S45-7
44. Sloan PA, Moulin DE, Hayes H. A clinical evaluation of transdermal therapeutic system fentanyl for the treatment of cancer pain. J Pain Symptom Manage 1998; 16: 102-11
45. Maves TJ, Barcellos WA. Management of cancer pain with transdermal fentanyl: phase IV trial, University of Iowa. J Pain Symptom Manage 1992; 7 Suppl. 3: S58-62
46. Simmonds MA, Richenbacher J. Transdermal fentanyl: long-term analgesic studies. J Pain Symptom Manage 1992; 7: S36-9
47. Coyle N, Adelhart J, Foley KM, et al. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. J Pain Symptom Manage 1990; 5: 83-93
48. Galer BS, Coyle N, Pasternak GW, et al. Individual variability in the response to different opioids: report of five cases. Pain 1992; 49: 87-91
49. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995; 10: 378-84
50. Bruera E, Pereira J, Watanabe S, et al. Opioid rotation in patients with cancer pain: a retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. Cancer 1996; 78: 852-7
51. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. Cancer 1999; 86: 1856-66
52. Ahmedzai S, Allan E, Fallon M, et al. Transdermal fentanyl in cancer pain. J Drug Dev 1994; 6: 93-7
53. Slappendel R, Lako SJ, Crul BJP. Gastrointestinal side effects diminish after switch over from morphine to transdermal fentanyl [abstract P1004]. Ann Oncol 1994; 5 Suppl. 8: 200
54. Hanks GW, de Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001; 84: 587-93
55. Kornick CA, Santiago-Palma J, Khojainova N. A safe and effective method of converting cancer patients from intravenous to transdermal fentanyl. J Pain 2001; 2 Suppl. 1: S35
56. Fudin J, Toledo-Binette C, Kupiak DM, et al. Quicker dosage adjustment for transdermal fentanyl. Am J Health Syst Pharm 1997; 54: 87-8
57. Vielvoye-Kerkmeer AP, Mattern C, Uitendaal MP. Transdermal fentanyl in opioid-naive cancer pain patients: an open trial using transdermal fentanyl for the treatment of chronic cancer pain in opioid-naîve patients and a group using codeine. J Pain Symptom Manage 2000; 19: 185-92
58. Radbruch L, Sabatowski R, Petzke F, et al. Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. Palliat Med 2001; 15: 309-21
59. Wong JO, Chiu GL, Tsao CJ, et al. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. Acta Anaesthesiol Sin 1997; 35: 25-32
60. Elsner F, Radbruch L, Sabatowski R, et al. Switching opioids to transdermal fentanyl in a clinical setting. Schmerz 1999; 13: 273-8
61. Portenoy RK. Chronic opioid therapy in nonmalignant pain. J Pain Symptom Manage 1990; 5: S46-62
62. Acute Pain Management Guideline Panel. Acute pain management: operative or medical procedures and trauma: clinical practice guideline. Rockville (MD): Agency for Health Care and Policy Research, Public Health Service, US Department of Health and Human Services; 1992 Feb. AHCPR publication #92-0032
63. Jacox A, Carr DB, Payne R, et al. Management of cancer pain: clinical practice guideline 9. Rockville (MD): Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services; 1994 Mar. AHCPR publication no. 4-0592
64. Moulin D, Iezzi A, Amireh R, et al. Randomized trial of oral morphine for chronic non-cancer pain. Lancet 1996; 347: 143-7
65. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986; 25: 171-86
66. Portenoy R. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996; 11: 203-17
67. Turk DC. Clinicians' attitude about prolonged use of opioids and the issue of patient heterogeneity. J Pain Symptom Manage 1996; 11: 218-30
68. Brena SF, Sanders SH. Opioids in nonmalignant pain: questions in search of answers. Clin J Pain 1991; 7: 342-5
69. Burchman SL, Pagel PS. Implementation of a formal treatment agreement for outpatient management of chronic pain with opioid analgesics. J Pain Symptom Manage 1995; 10: 556-63
70. Bannwarth B. Risk-benefit assessment of opioids in chronic non-cancer pain. Drug Saf 1999; 21 (4): 283-96
71. Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. J Pain Symptom Manage 1993; 8: 279-88
72. Barkin RL, Lubenow TR, Bruehl S, et al. Management of chronic pain: part I and part II. Dis Mon 1996; 42: 385-456
73. Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain 2001; 2: 197-204
74. Sandler AN, Baxter AD, Katz J, et al. A double-blind, placebo-controlled trial of transdermal fentanyl after abdominal hysterectomy: analgesic, respiratory, and pharmacokinetic effects. Anesthesiology 1994; 81: 1169-80
75. Bulow HH, Linnemann M, Berg H, et al. Respiratory changes during treatment of postoperative pain with high dose transdermal fentanyl. Acta Anaesthesiol Scand 1995 Aug; 39 (6): 835-9
76. Food and Drug Administration (FDA). Fentanyl transdermal system approved for chronic pain. JAMA 1990; 264: 1802
77. Vecchione A. Fentanyl linked to patient death in Nevada hospital. Hospital Pharmacist Report 1995; 12: 11
78. A woman sues over painkiller patch [newspaper article]. Persxx Times 1993 Nov 15: 4B
79. Strupp C, Sudhoff T, Germing U, et al. Transdermal fentanyl during high-dose chemotherapy and autologous stem cell support. Oncol Rep 2000; 7: 659-61
80. Mantovani G, Currell L, Macció A, et al. Prevention of nausea and vomiting (N&V) in cancer patients receiving high-dose cisplatin: assessment of the potential antiemetic activity of transdermal fentanyl (TTS-F) compared to standard antiemetic

treatment in acute and delayed N&V: first clinical report. Anticancer Res 1999; 19: 3495-502
81. Korte W, de Stoutz N, Morant R. Day-to-day titration to initiate transdermal fentanyl in patients with cancer pain: short- and long-term experiences in a prospective study of 39 patients. J Pain Symptom Manage 1996; 11: 139-46
82. Jeal W, Benfield P. Transdermal fentanyl: a review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 1997; 53 (1): 109-38
83. Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology 2000; 14: 695-705
84. Foley KM. The treatment of cancer pain. N Engl J Med 1985; 313: 84-95
85. Ashburn MA, Lipman AG. Management of pain in the cancer patient. Anesth Analg 1993; 76: 402-16
86. Lawlor P, Turner K, Hanson J, et al. Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. Pain 1997; 72: 79-85
87. Lawlor PG, Turner KS, Hanson J, et al. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer 1998; 82: 1167-73
88. Kornick CA, Santiago-Palma J, Schulman G, et al. A safe and effective method for converting patients from transdermal to intravenous fentanyl for the treatment of acute cancer-related pain. Cancer 2003; 97: 3121-4
89. Payne R, Chandler S, Einhaus M. Guidelines for the clinical use of transdermal fentanyl. Anticancer Drugs 1995; 6 Suppl. 3: 50-3
90. Donner B, Zenz M, Tryba M, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain 1996; 64: 527-34
91. Brooks D. Day-to-day titration of transdermal fentanyl is unwise [letter; comment]. Support Care Cancer 1995; 3: 210-1
92. Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. Ann Pharmacother 1995; 29: 969-71
93. The TTS Fentanyl Multicentre Study Group. Transdermal fentanyl in cancer pain. J Drug Dev 1994; 6: 93-7
94. Payne R. Factors influencing quality of life in cancer patients: the role of transdermal fentanyl in the management of pain. Semin Oncol 1998; 25 (3 Suppl. 7): 47-53
95. Radbruch L, Sabatowski R, Loick G, et al. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. Palliat Med 2000; 14: 111-9
96. Alsahaf MH, Stockwell M. Respiratory failure due to the combined effects of transdermal fentanyl and epidural bupivacaine/diamorphine following radical nephrectomy. J Pain Symptom Manage 2000; 20: 210-3
97. Bernstein KZ, Klausner MA. Potential dangers related to transdermal fentanyl (Duragesic) when used for postoperative pain [letter; comment]. Dis Colon Rectum 1994; 37: 1339-40
98. Bernstein KJ. Inappropriate use of transdermal fentanyl for acute postoperative pain [letter]. J Oral Maxillofac Surg 1994; 52: 896
99. Rose PG, Macfee MS, Boswell MV. Fentanyl transdermal system overdose secondary to cutaneous hyperthermia. Anesth Analg 1993; 77: 390-1
100. Frölich M, Giannotti A, Modell JH. Opioid overdose in a patient using a fentanyl patch during treatment with a warming blanket. Anesth Analg 2001; 93: 647-8
101. Newshan G. Heat-related toxicity with the fentanyl transdermal patch. J Pain Symptom Manage 1998; 16: 277-8
102. Hardwick Jr WE, King WD, Palmisano PA. Respiratory depression in a child unintentionally exposed to transdermal fentanyl patch. South Med 1997; 90: 962-4
103. Klockgether-Radke A, Hildebrandt J. Opioidintoxikation. Unsachgemässe Anwendung von transdermalem Fentanyl. Anaesthesist 1997; 46: 428-9
104. Flannagan LM, Butts JD, Anderson WH. Fentanyl patches left on dead bodies: potential source of drug for abusers. J Forensic Sci 1996; 41: 320-1
105. Marquardt KA, Tharratt RS. Inhalation abuse of fentanyl patch. Clin Toxicol 1994; 32: 75-8
106. DeSio JM, Bacon DR, Peer G, et al. Intravenous abuse of transdermal fentanyl therapy in a chronic pain patient. Anesthesiology 1993; 79: 1139-41
107. Kramer C, Tawney M. A fatal overdose of transdermally administered fentanyl. J Am Osteopath Assoc 1998; 98: 385-6
108. Edinboro LE, Poklis A, Trautman D, et al. Fatal fentanyl intoxication following excessive transdermal application. J Forensic Sci 1997; 42: 741-3
109. Davies AN, Bond C. Transdermal fentanyl and the opioid withdrawal syndrome [letter]. Palliat Med 1996; 10: 348
110. Higgs CM, Vella-Brincat J. Withdrawal with transdermal fentanyl [letter; comment]. J Pain Symptom Manage 1995; 10: 4-5
111. Zenz M, Donner B, Strumpf M. Withdrawal symptoms during therapy with transdermal fentanyl (fentanyl TTS)? J Pain Symptom Manage 1994; 9: 54-5
112. Han PKJ, Arnold R, Bond G, et al. Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. J Pain Symptom Manage 2002; 23: 66-72
113. Kuzma PJ, Kline MD, Stamatos JM, et al. Acute toxic delirium: an uncommon reaction to transdermal fentanyl. Anesthesiology 1995; 83: 869-71
114. Steinberg RB, Gilman DE, Johnson III F. Acute toxic delirium in a patient using transdermal fentanyl. Anesth Analg 1992; 75: 1014-6
115. Song CW, Chelstron LM, Sevit SH, et al. Effects of temperature on blood circulation with laser Doppler method. Int J Radiat Oncol Biol Phys 1989; 17: 1041-7
116. US Department of Health and Human Services. The 2001 DAWN report: narcotic analgesics [online]. Available from URL: http://www.samhsa.gov/oas/dawn.htm [Accessed 2003 Aug 26]
117. Calis KA, Kohler DR, Corso DM. Transdermally administered fentanyl for pain management. Clin Pharm 1992; 11: 22-36
118. Ferrell BR, Griffith H. Cost issues related to pain management: report from the cancer pain panel of the agency for healthcare policy and research. J Pain Symptom Manage 1994; 9: 221-34
119. Neighbors DM, Bell TJ, Wilson J, et al. Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain. J Pain Symptom Manage 2001; 21: 129-43

Correspondence and offprints: Dr *Craig A. Kornick*, Riverside Spine and Pain Physicians, P.L. Suite 4-5, 4339 Roosevelt Blvd, Jacksonville, FL 32210, USA.
E-mail: kornick@riversidespine.com