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Fentanyl Transdermal Matrix Patch (Durotep® MT Patch; Durogesic® DTrans®; Durogesic® SMAT)

In Adults with Cancer-Related Pain

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Contents

Abstract

▲ The fentanyl transdermal matrix patch is approved in Japan for the management of moderate to severe cancer-related pain in adults.

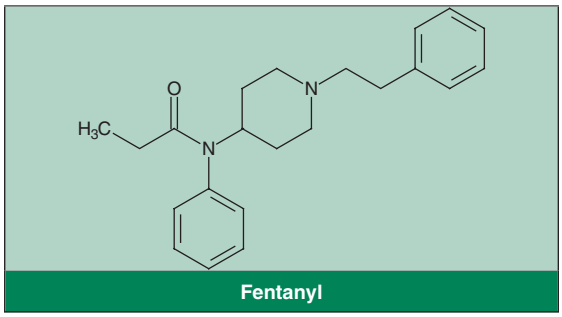
▲ Bioequivalence, in terms of exposure and the maximum and minimum serum concentrations, has been established between the fentanyl transdermal matrix patch 16.8 mg (100 μg/h) and the fentanyl transdermal reservoir patch 10 mg (100 μg/h) after single and multiple applications.

▲ The fentanyl transdermal matrix patch 2.1–8.4 mg (12.5–50 μg/h) effectively managed chronic cancer-related pain in adults in a noncomparative, multicentre, phase II study; 89.4% of recipients rated their global assessment of pain as 'very satisfied', 'satisfied' or 'neither satisfied nor dissatisfied'.

▲ Adults with cancer- or non-cancer-related chronic pain were switched from fentanyl transdermal reservoir patch to fentanyl transdermal matrix patch therapy without compromising efficacy; no differences in pain intensity or sleep interference scores were seen between the two formulations in an nonblind, multicentre, switching pilot study.

▲ Given the nature of the therapy, the tolerability profile of the fentanyl transdermal matrix patch was generally acceptable. Topical adverse events included erythema, application-site irritation and pruritus. In general, patients and physicians preferred the fentanyl transdermal matrix patch over the fentanyl transdermal reservoir patch in the pilot study.

Features and properties of the fentanyl transdermal matrix patch	
Indication	
Moderate to severe cancer-related pain in adults	
Mechanism of action	
μ-Opioid-receptor agonist	
Dosage and administration	
Dose delivered over a 72-hour	2.1 mg (12.5 μg/h; 5.25 cm^2)
period (release rate; patch	4.2 mg (25 μg/h; 10.5 cm^2)
surface area)	8.4 mg (50 μg/h; 21.0 cm^2)
	12.6 mg (75 μg/h; 31.5 cm^2)
	16.8 mg (100 μg/h; 42.0 cm^2)
Route of administration	Transdermal
Frequency of administration	72 h
Pharmacokinetic profile of the fentanyl transdermal matrix patch 16.8 mg (at steady state) in healthy volunteers; mean values unless stated otherwise	
Maximum serum concentration (C_{max})	4.8 ng/mL
Median time to C_{max}	24.0 h
Minimum serum concentration (C_{min})	1.68 ng/mL
Median time to C_{min}	5.0 h
Area under the serum concentration-time curve from time 216 to 288 hours	216.2 ng • h/mL
Half-life	24.8 h
Most frequent treatment-emergent adverse events	
Nausea, somnolence, vomiting, diarrhoea, constipation	



Approximately 60% of patients with cancer experience pain.[1] The mainstay of cancer-related pain management is opioid-based therapy,[2] with the transdermal administration of opioids a valuable therapy option because it permits a constant rate of drug release, thus maintaining stable drug concentrations, and a convenient dosing regimen.[3] Fentanyl is a high potency opioid agonist that is suitable for transdermal administration owing to its high lipid solubility.[4]

The early transdermal administration of fentanyl was achieved via a reservoir patch.[5] This patch is, however, associated with significant interindividual variability; 60–84% of the fentanyl is absorbed in the majority of patients, although absorption is <60% in one-third of patients and >84% in approximately 9% of patients.[6] Furthermore, a defect in, or a violation of, the rate-limiting membrane can result in 'dose dumping' or a fatal overdose.[6] This also allows the potential for misuse.[7]

Recent advances in transdermal technology permitted the redesign of the fentanyl transdermal reservoir patch in order to improve its structure, composition and release profile.[5] The result is the fentanyl transdermal matrix patch (Durotep® MT Patch; Durogesic® DTrans®; Durogesic® SMAT),[1] which consists of a drug-in-adhesive matrix layer (initially covered with a liner) and a backing layer (figure 1).[8]

The fentanyl transdermal matrix patch was designed to be bioequivalent to the original reservoir patch and to constantly and reliably deliver fentanyl.[5] However, compared with the reservoir patch, the fentanyl in the matrix patch is entirely dissolved in the adhesive, thus, opioid dissolution is not required prior to its diffusion through the matrix following application.[5] Moreover, rate-controlling mechanisms and permeability enhancers are not required as the matrix and the patient's stratum corneum control the systemic delivery rate.[5] The matrix patch also has better flexibility and skin conformability, and produces linear fentanyl dose kinetics with negligible dose loading.[5,6]

The fentanyl transdermal matrix patch is approved in Japan for the management of moderate to severe cancer-related pain in adult patients and is currently available in five different strengths: (i) a 2.1 mg patch delivering 12.5 μg/hour; (ii) a 4.2 mg patch delivering 25 μg/hour; (iii) a 8.4 mg patch delivering 50 μg/hour; (iv) a 12.6 mg patch delivering 75 μg/hour; and (v) a 16.8 mg patch delivering 100 μg/hour.[8] It has also been approved in the UK[9] and various other countries worldwide for the management of cancer- or non-cancer-related chronic pain, although a detailed discussion of its efficacy in the latter indication and in paediatric patients is beyond the scope of this review. This profile focuses on the pharmacological and clinical efficacy and tolerability data relevant to the use of the fentanyl transdermal matrix patch in the management of moderate to severe cancer-related pain in adult patients.

1. Pharmacodynamic Profile

The pharmacodynamic properties of fentanyl are well established and have been discussed in detail previously;[4,10] therefore, this section provides a brief overview of data relevant to the management of patients with cancer-related pain.

Opioids mediate their effects via three opioid receptors, designated μ, δ and κ,[11-13] with the μ-opioid receptor existing as two pharmacologically distinct subtypes: μ_1 and μ_2.[14,15] Activation of each opioid receptor induces a number of effects, including supraspinal (mediated by μ_1-, δ- and κ-opioid

1 The use of trade names is for product identification purposes only and does not imply endorsement.

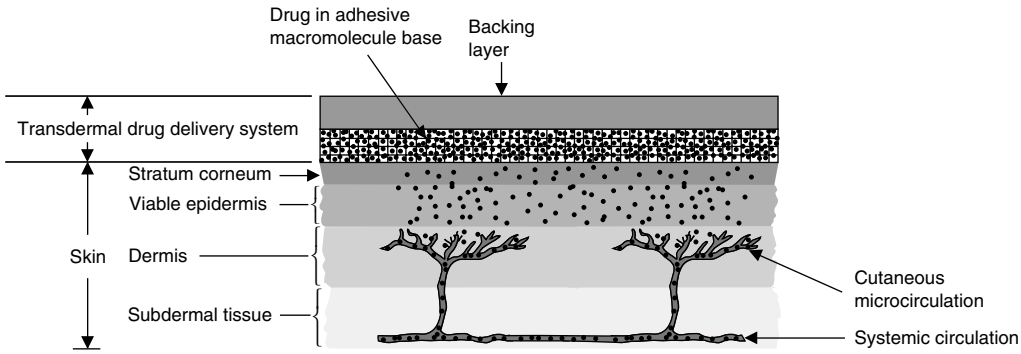


Fig. 1. Structure of the fentanyl transdermal matrix patch.

receptors) and spinal (μ, δ and κ) analgesia, reduced gastrointestinal tract motility (μ_2 and κ), sedation (μ and κ) and respiratory depression (μ_2 and κ).[16,17]

- Fentanyl is a highly potent synthetic opioid agonist; it binds with high affinity to the μ-opioid receptor, exhibiting low δ- and κ-opioid receptor affinity.[4,18] Furthermore, *in vivo* data indicate that fentanyl- and morphine-induced antinociception (at both the supraspinal and spinal levels) is mediated primarily via the μ_1-opioid receptor.[19] There appears to be different μ_1-opioid receptor subtypes, with preliminary data implicating a morphine-insensitive μ_1-opioid receptor subtype in fentanyl-induced antinociception.[20]

- The majority of the pharmacological effects of fentanyl occur in the CNS, with opioid receptors located at numerous points along the pain pathways of the mammalian CNS.[4]

- The analgesic potency of fentanyl is approximately 75- to 100-fold greater than that of morphine;[21] this difference may be a reflection of the lipophilic nature of fentanyl, which enables its rapid transfer across the blood-brain barrier.[22,23]

- As with other opioids, fentanyl may induce potentially life-threatening respiratory depression.[4] While such respiratory effects are believed to be mediated by the μ_2-opioid receptor,[17] the respiratory effects of fentanyl, but not morphine, were reversed by the selective μ_1-opioid antagonist naloxonazine in one *in vivo* study, indicating that the μ_1-opioid receptor may also play a role in fentanyl-induced respiratory depression.[24]

- A 30-day, randomized, nonblind, crossover, multicentre study in 202 patients with chronic cancer-related pain suggests that fentanyl is less sedative than morphine, with significantly ($p < 0.05$) less daytime drowsiness (as assessed by a visual analogue scale) observed with a fentanyl transdermal reservoir patch (starting dose: 25–300 μg/h) than with sustained-release oral morphine. Patients received the fentanyl transdermal reservoir patch (starting dose: 25–300 μg/h; calculated using a dosage conversion table supplied by the manufacturer) every 72 hours for 15 days or sustained-release oral morphine every 12 hours for 15 days in a crossover manner.[25]

- Opioid administration frequently induces constipation.[26] The binding of opioids to receptors in the gastrointestinal tract leads to a reduction in peristalsis and biliary, intestinal and pancreatic secretions, and an elevation in anal and ileocaecal tone, thereby lowering stool hydration and increasing colonic transit times.[26]

2. Pharmacokinetic Profile

The pharmacokinetic properties of the fentanyl transdermal matrix patch have been compared with those of the fentanyl transdermal reservoir patch in two randomized, nonblind, crossover, single-centre studies in healthy men and women aged 18–45 years.[5] In the first study (study 1; n = 38), volunteers received either the fentanyl transdermal matrix patch 16.8 mg for 72 hours followed by the fentanyl transdermal reservoir patch 10 mg (100 μg/

h) for 72 hours followed by a repeat of this sequence, or the fentanyl transdermal reservoir patch 10 mg for 72 hours followed by the fentanyl transdermal matrix patch 16.8 mg for 72 hours followed by a repeat of this sequence.[5] In the second study (study 2; n = 42), volunteers received the fentanyl transdermal matrix patch 16.8 mg for 72 hours for four consecutive applications (total 288 hours) or the fentanyl transdermal reservoir patch 10 mg for 72 hours for four consecutive applications (total 288 hours) in a crossover manner.[5] In both studies, each treatment was applied to a different site on the upper outer arm of the volunteer, with a minimum washout period of 6–14 days between the two treatments.[5] Twice-daily oral naltrexone 50 mg was administered (from 14 hours prior until 24 hours after application) to attenuate the opioid effects of fentanyl.[5]

Bioequivalence of the fentanyl transdermal matrix patch with the fentanyl transdermal reservoir patch was established if, for the area under the serum concentration-time curve (AUC) [studies 1 and 2], the maximum serum concentration (C_{max}) [studies 1 and 2] and the minimum serum concentration (C_{min}) [study 2], the 90% confidence interval (CI) of the least squares estimates of the fentanyl transdermal matrix patch : fentanyl transdermal reservoir patch ratio was within the range 80–125%.[5] Least squares estimates were transformed logarithmically.[5] Bioequivalence was specifically estimated during the fourth application period of each treatment in study 2.[5] Intra- and inter-subject variability was also assessed in study 1.[5]

Additional data on the pharmacokinetic properties of the fentanyl transdermal matrix patch were obtained from the Japanese[8] and UK[9] manufacturer's prescribing information. Where data for certain pharmacokinetic properties are not available for the fentanyl transdermal matrix patch, those for the fentanyl transdermal reservoir patch (which have been reviewed previously in *Drugs*[4]) are discussed. Data are reported as mean values unless otherwise stated.

Absorption and Distribution

- Serum fentanyl concentrations increased in a dose-dependent manner after the application of fentanyl transdermal matrix patches to Japanese patients with cancer-related pain; the initial dosage was 2.1 mg adjusted to a maximum of 8.4 mg.[8]
- In healthy volunteers, C_{max} was positively correlated with the dose following a single 72-hour application of the fentanyl transdermal matrix patch 4.2–16.8 mg ($p < 0.0001$).[8]
- Following the first 72-hour application of the fentanyl transdermal matrix patch 16.8 mg in healthy volunteers (study 1), AUC from time zero to 72 hours (AUC_{72}), AUC from time zero to infinity (AUC_{∞}), C_{max} and median time taken to reach C_{max} (t_{max}) values were 159.4 ng • h/mL, 211.8 ng • h/mL, 3.48 ng/mL and 24.2 hours, respectively.[5] Corresponding values for the fentanyl transdermal reservoir patch 10 mg were 133.6 ng • h/mL, 176.2 ng • h/mL, 3.04 ng/mL and 42.2 hours.[5]
- Steady-state conditions for the fentanyl transdermal matrix patch are reached within the second 72-hour application period.[9] After four consecutive applications of the fentanyl transdermal matrix patch 16.8 mg (study 2), AUC from time 216 to 288 hours ($AUC_{216–288}$), C_{max} and C_{min} values (for the fourth application period) were 216.2 ng • h/mL, 4.8 ng/mL and 1.68 ng/mL, respectively.[5] The corresponding values for the fentanyl transdermal reservoir patch 10 mg were 190.1 ng • h/mL, 4.57 ng/mL and 1.50 ng/mL.[5]
- Median t_{max} and time taken to reach C_{min} values at the fourth application period in study 2 were 24.0 and 5.0 hours for both patch formulations; fluctuation (the difference between C_{max} and C_{min} values compared with the mean concentration during the fourth application period) was 101.8% for the fentanyl transdermal matrix patch 16.8 mg and 109.0% for the fentanyl transdermal reservoir patch 10 mg.[5]
- Bioequivalence between the fentanyl transdermal matrix patch and the fentanyl transdermal reservoir patch was demonstrated after a single application (study 1) and at steady state (study 2), as determined by the prespecified equivalence condi-

tions.[5] The fentanyl transdermal matrix patch : fentanyl transdermal reservoir patch ratios were 114.54% (90% CI 109.52, 119.78) for AUC_{72}, 115.28% (90% CI 110.32, 120.46) for AUC_{∞} and 108.58% (90% CI 102.29, 115.25) for C_{max} in study 1, and 109.26% (90% CI 102.49, 116.48) for $AUC_{216–288}$, 106.23% (90% CI 95.56, 118.09) for C_{max} and 106.61% (90% CI 98.96, 114.85) for C_{min} in study 2.[5]

- Inter- and intra-subject variability (study 1) was generally low for both the fentanyl transdermal matrix patch 16.8 mg and the fentanyl transdermal reservoir patch 10 mg (coefficient of variation <30%), with slightly greater inter- versus intra-subject variability observed.[5]
- Fentanyl is ≈84% protein bound in plasma.[8] In rats, radiolabelled fentanyl was widely distributed into the bone marrow, kidneys, lungs, liver, nasal mucosa, pancreas, reproductive system and spleen, and into the urine and duodenal contents following subcutaneous injections.[8]

Metabolism and Elimination

- Fentanyl primarily undergoes hepatic metabolism via the cytochrome P450 (CYP) 3A4 isoenzyme; oxidative *N*-dealkylation of the piperidine ring of fentanyl produces the metabolite norfentanyl.[4,8] Norfentanyl and other (minor) metabolites, including despropionylfentanyl, hydroxyfentanyl and hydroxynorfentanyl, have negligible pharmacological activity.[4]
- Fentanyl and its metabolites are predominately (≈76%) excreted in the urine, with ≈6.4% of the dose excreted as unchanged drug.[8] Faecal excretion accounts for ≈9% of the fentanyl dose.[8]
- The half-life ($t_{1/2}$) after a single application of the fentanyl transdermal matrix patch 16.8 mg versus the fentanyl transdermal reservoir patch 10 mg was 22.1 and 20.6 hours (study 1); corresponding $t_{1/2}$ values at steady state were 24.8 and 23.4 hours (study 2).[5]

Special Patient Groups

- In a study in elderly (aged 65–81 years) [n = 21] and adult (aged 18–33 years) [n = 27] healthy volunteers, C_{max} values of 2.48 and 2.69 ng/mL were reached 49.7 and 35.1 hours after a single application of the fentanyl transdermal matrix patch 16.8 mg for 72 hours.[8] AUC from time zero to 120 hours and AUC values were 153.3 and 190.1 ng • h/mL for the elderly volunteers, and 164.1 and 177.8 ng • h/mL for adult volunteers; $t_{1/2}$ values were 34.4 versus 23.9 hours.[8]
- The AUC from time zero to 144 hours (AUC_{144}) and C_{max} of fentanyl was 1.73- and 1.35-fold greater in patients with postoperative pain and cirrhosis (n = 9; age 39–66 years) than in the control group (n = 8; age 30–65 years) [no further details reported] after a single 72-hour application of the fentanyl transdermal matrix patch 8.4 mg (AUC_{144} 123.0 vs 71.0 ng • h/mL; C_{max} 1.52 vs 1.13 ng/mL).[8] In the corresponding patient groups, t_{max} was 40 versus 33 hours and $t_{1/2}$ was 19.8 versus 20.6 hours.[8]

Drug Interactions

- Concurrent treatment with CYP3A4 inhibitors (e.g. amiodarone, clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, nelfinavir, ritonavir, verapamil) may elevate plasma fentanyl concentrations, thereby elevating or prolonging both therapeutic effects and adverse events and resulting in serious respiratory depression.[8,9] Therefore, the administration of concomitant transdermal fentanyl and CYP3A4 inhibitor therapy is not recommended; frequent monitoring is necessary in patients receiving concurrent therapy.[8,9]

3. Therapeutic Efficacy

The efficacy of the fentanyl transdermal matrix patch has been assessed over 6[27] and 9[28] days in adult patients with chronic cancer-related pain in a noncomparative, multicentre, phase II study (n = 85)[27] and in adult patients with cancer- or non-cancer-related chronic pain in an nonblind, multicentre, switching pilot study (n = 46).[28]

Where described, the studies enrolled male and female adult (aged ≥20[27] or 18–75[28] years) patients who had a confirmed diagnosis of cancer,[27] pain intensity scores (visual analogue scale) ≤34 mm[27] and were receiving either a stable dose of transdermal fentanyl (reservoir system)[28] or stable low-dose daily analgesia (except rescue medication) for ≥3 days prior to study entry, including morphine (oral: <45 mg/day; suppository: <30 mg/day; injection [route not stated]: <15 mg/day), oral oxycodone <30 mg/day or fentanyl injection (route not stated) <0.3 mg/day.[27]

Patient exclusion criteria varied between the studies and, where stated, included active skin disease,[28] age <18 or >75 years,[28] asthma,[27] bradyarrhythmia,[27] a history of[27] or current drug dependency,[27,28] a high sensitivity to fentanyl or other opioid analgesics,[27] a history of drug abuse,[27] opioid intolerance,[28] pregnancy,[28] psychiatric illness,[28] or a severe[28] cardiovascular,[28] hepatic,[27,28] metabolic,[28] renal[27,28] or respiratory[27,28] disorder.

Patients in the phase II study received the fentanyl transdermal matrix patch 2.1 mg at baseline (day 1); each patch was applied to the chest or upper arm of the patient for 72 hours.[27] On days 4 and 7 (72 hours after application of the previous patch), the patch was replaced, with the dose increased as required (based on the use of rescue medication and an evaluation of pain intensity) from 2.1 to 4.2 mg, from 4.2 to 6.3 mg or from 4.2 to 8.4 mg.[27] Approximately 67% of patients (57 of 85) received fentanyl transdermal matrix patches 2.1 mg throughout the phase II study.[27] Patients experiencing breakthrough pain or severe uncontrolled baseline pain were administered an equivalent dose of oral fast-acting morphine (e.g. patients receiving the fentanyl transdermal matrix patch 2.1 mg were administered an oral equivalent 5 mg dose of morphine).[27]

Patients in the pilot study received a fentanyl transdermal reservoir patch (patch size equivalent to previously used systems; no other data reported) at baseline, followed 48 (only those patients whose pain therapy was changed every 48 hours prior to study entry) or 72 hours later by a fentanyl transdermal matrix patch (with an equivalent release rate to the reservoir patch). The fentanyl transdermal matrix patch was removed ≈72 hours later and a second matrix patch applied.[28] The median transdermal fentanyl dose throughout the pilot study was 8.4 mg.[28]

Where stated, the use of opioid therapy (apart from the rescue medication)[28] or other medications (including opioid receptor antagonist analgesics, non-opioid analgesics, NSAIDs or opioid antagonists)[27] was not permitted in the two studies.[27,28] However, patients in the phase II study receiving a stable dose of non-opioid analgesics or NSAIDs prior to study entry were permitted to continue concomitant therapy throughout the study.[27]

Patients had a mean age of 66.5[27] or 59.2[28] years and a mean duration of pain of 5.7[27] or 54.0[28] months. Patients in the phase II study (n = 85) had Eastern Cooperative Oncology Group performance status scores at study entry of 0 (15.3% of patients), 1 (38.8%), 2 (28.2%), 3 (16.5%) or 4 (1.2%), and were previously receiving morphine (29.4%), oxycodone (69.4%) or fentanyl (1.2%).[27] Patients in the pilot study (n = 46) had been receiving transdermal fentanyl reservoir patch 2.5 mg (25 μg/h) [20% of patients], 5 mg (50 μg/h) [34%], 7.5 mg (75 μg/h) [7%], 10 mg (100 μg/h) [9%], 12.5 mg (125 μg/h) [4%], 15 mg (150 μg/h) [9%] or ≥15 mg (≥150 μg/h) [17%] therapy for a mean of 24 months, and had cancer- (48%) or non-cancer-related (52%) chronic pain.[28]

The primary endpoint in the phase II study was the patient's global assessment of pain (scale 1–5; 1 = very dissatisfied, 5 = very satisfied; a score of ≥3 was defined as effective) at study end (day 10) or discontinuation.[27] Secondary endpoints included the patient's global assessment of pain on days 1, 4 and 7, the physician's global assessment of pain (scale 1–2; 1 = effective, 2 = ineffective) at study end or discontinuation, pain intensity (visual analogue scale), total duration of pain per day and the use of rescue medication (morphine).[27] Endpoints were not specified as primary or secondary in the pilot study and included pain intensity (mean, minimum and maximum) over the previous 24 hours

(numeric rating scale [NRS] 0–10; 0 = no pain, 10 = worst possible pain), sleep interference over the previous 24 hours (NRS 0–10; 0 = pain does not interfere with sleep, 10 = pain completely interferes with sleep) and the use of rescue medication.[28]

Data are reported for the intent-to-treat[27,28] and per-protocol[27] populations.

Phase II Study

- In the phase II study (n = 85), 89.4% of fentanyl transdermal matrix patch recipients rated their global assessment of pain as ≥3 (i.e. 'very satisfied', 'satisfied' or 'neither satisfied nor dissatisfied') [primary endpoint].[27] Subgroup analysis revealed that patient global assessment scores of ≥3 were achieved in 92.0%, 89.8% and 0% of patients previously receiving morphine (n = 25), oxycodone (n = 59) or fentanyl (n = 1).[27] Elevations in the number of patients achieving a patient's global assessment score of 'very satisfied' or 'satisfied' was observed over time (no quantitative data or statistical analysis reported).[27]
- In terms of physician global assessment, the fentanyl transdermal matrix patch was rated as 'effective' in 92.0%, 96.6% and 0% of patients previously receiving morphine (n = 25), oxycodone (n = 59) or fentanyl (n = 1).[27]
- The use of rescue medication throughout the phase II study appeared to remain relatively constant (no quantitative data reported).[27] In the per-protocol population, up to 26 patients required rescue medication, with the highest daily dose ranging from 15 to 40 mg.[27]

Pilot Study

- Patients in the pilot study were switched from fentanyl transdermal reservoir patch to fentanyl transdermal matrix patch therapy without compromising efficacy, as observed by the lack of differences in pain intensity or sleep interference scores between the two formulations.[28] For example, the changes in the mean, minimum and maximum pain intensity scores from baseline (the average of the mean, minimum and maximum scores in the fentanyl transdermal reservoir patch treatment period) to study end (the average of the mean, minimum and maximum scores during the second fentanyl transdermal matrix patch treatment period) were −0.24, −0.08 and −0.15, respectively.[28]
- No significant differences in mean, minimum and maximum pain scores on days 2, 5, 6, 8 and 9 were observed between those patients who received pain therapy every 48 hours (n = 13) and those who received pain therapy every 72 hours (n = 33) prior to study entry.[28]
- The use of rescue medication in the pilot study was generally similar with regard to frequency and type among patients applying the fentanyl transdermal matrix patch compared with those applying the fentanyl transdermal reservoir patch (no statistical analysis reported).[28]

4. Tolerability

Data concerning the tolerability of the fentanyl transdermal matrix patch were primarily obtained from the noncomparative, multicentre, phase II study in adults with chronic cancer-related pain (n = 86)[27] and the nonblind, multicentre, switching pilot study in adults with cancer- or non-cancer-related chronic pain (n = 46)[28] discussed in section 3. Patient and physician preferences in the pilot study are also discussed.[28] The irritation potential of the fentanyl transdermal matrix patch was also examined in a randomized, single-blind, crossover study in healthy volunteers (n = 45) aged 50–75 years who received a single application of fentanyl transdermal matrix patch 4.2 mg or transdermal buprenorphine patch 35 μg/h, each for 72 hours.[3] Naltrexone 50 mg/day was administered to the volunteers on days 1 and 4 (30 or 60 minutes prior to patch application) and on days 2, 3, 5 and 6 to antagonize the pharmacological effects of fentanyl and buprenorphine.[3]

General Adverse Events

- Given the nature of the therapy, the tolerability profile of the fentanyl transdermal matrix patch was generally acceptable. In the phase II study, the most frequently reported (≥15%) treatment-emergent ad-

verse events in adult patients receiving the fentanyl transdermal matrix patch included nausea, somnolence, vomiting, diarrhoea and constipation (figure 2).[27] Respiratory failure and dyspnoea were observed in 3.5% of patients in the phase II study.[27]

- In the phase II study, 316 adverse events were reported in 90.7% (78 of 86) of the fentanyl transdermal matrix patch recipients.[27] Constipation, nausea, somnolence and vomiting were observed in 8.1%, 11.6%, 16.3% and 7.0% of patients, respectively, at baseline (at which time patients were receiving stable low-dose daily morphine, oxycodone or fentanyl for at least 3 days prior to study entry), 11.6%, 16.3%, 18.6% and 12.8% of patients after application of the first fentanyl transdermal matrix patch, 1.2%, 6.0%, 6.0% and 12.0% of patients after application of the second matrix patch, and 3.8%, 11.4%, 10.1% and 10.1% of patients after application of the third matrix patch (no statistical analysis reported).[27]
- In the pilot study, pruritus occurred significantly less frequently with the fentanyl transdermal matrix patch than with the fentanyl transdermal reservoir patch (29% vs 48% of patients; $p < 0.05$).[28] There was no significant difference between the matrix and reservoir patches in the incidence of somnolence (83% vs 83%), dry mouth (71% vs 76%), sweating (66% vs 72%), constipation (51% vs 63%), nausea (29% vs 37%), micturition problems (29% vs 33%) and vomiting (12% vs 7%).[28] For the fentanyl transdermal matrix patch, adverse events were assessed on days 7–9 (i.e. during application of the second matrix patch).[28]

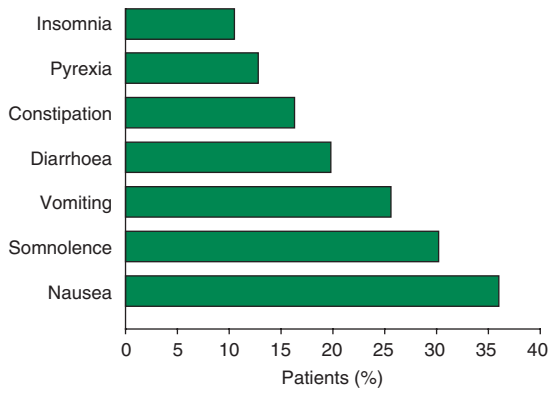


Fig. 2. Tolerability profile of the fentanyl transdermal matrix patch in adults with cancer-related pain. Incidence of treatment-emergent adverse events occurring in ≥10% of patients in a noncomparative, multicentre, phase II study (n = 86).[27] See section 3 for dosage and study design details.

- In the phase II study, three recipients of the fentanyl transdermal matrix patch experienced severe adverse events other than death.[27] Seven deaths occurred during the study, five of which were considered unrelated to the fentanyl transdermal matrix patch; of the remaining two deaths, the causal relationship with the fentanyl transdermal matrix patch was undetermined.[27] No serious or fatal adverse events occurred in the pilot study.[28]
- Treatment-emergent laboratory abnormalities reported in the phase II study included abnormal changes in γ-glutamyltransferase (12.0% of patients), alkaline phosphatase (10.7%), AST (8.3%), ALT (8.3%), total bilirubin (8.3%) and blood urea nitrogen (8.3%) levels, and in white blood cell (WBC) [11.9%] and platelet (8.3%) counts.[27] The majority of the laboratory abnormalities were deemed to be unrelated to fentanyl transdermal matrix therapy; only two (abnormal hepatic function in one patient and decreased WBC and platelet counts in another patient) were considered to be clinically significant/severe.[27]

Topical Adverse Events

- In the phase II study, application-site irritation and erythema occurred in 8.1% and 5.8% of fentanyl transdermal matrix patch recipients.[27]
- Blistering, reddening or weeping at the application site was observed significantly less frequently after the removal of the fentanyl transdermal matrix patch (at the end of the first [6%] and second [2%] application periods) versus the fentanyl transdermal reservoir patch (33%) [$p < 0.05$].[28]
- No significant difference in the incidence of erythema 60 minutes after patch removal was observed in the intent-to-treat population (n = 45) between fentanyl transdermal matrix patch versus buprenorphine transdermal patch recipients (75.6% vs 88.9%) [primary endpoint] in the randomized crossover study.[3] However, the incidence of erythema 72 hours after patch removal in the per-protocol

population (n = 41) and the mean erythema severity scores 60 minutes after patch removal in the intent-to-treat population (n = 45) were significantly ($p < 0.05$) lower in fentanyl transdermal matrix patch versus buprenorphine transdermal patch recipients.[3]

- Treatment-emergent topical adverse events were reported in one fentanyl transdermal matrix patch recipient (application-site pruritus) and six buprenorphine transdermal patch recipients (application-site pruritus [n = 2], allergic dermatitis [n = 2], exanthem [n = 1], generalized pruritus [n = 1]) in the randomized crossover study.[3]

Patient and Physician Preference

- Patient-rated adhesive properties, general satisfaction, skin compatibility and wearability/comfort scores (NRS 1–6; 1 = very good, 6 = insufficient) in the pilot study were significantly ($p < 0.05$) higher for the fentanyl transdermal matrix patch (at the end of both the first and second application periods [days 6 and 9]) versus the fentanyl transdermal reservoir patch (1.5–1.9 and 1.5–1.8 vs 2.5–3.2).[28]
- At study end (day 9), patient- and physician-rated scores for ease of use, general satisfaction, patient acceptance, skin compatibility and wearability/comfort (physicians did not score wearability/comfort and patients did not score patient acceptance) were <2 for the fentanyl transdermal matrix patch.[28] Patient- and physician-rated pain relief scores and physician-rated duration of analgesia scores were all between 2.1 and 2.3, with the duration of efficacy for the fentanyl transdermal matrix patch assessed by 87% of patients and 91% of physicians as being equal to or longer than that of the fentanyl transdermal reservoir patch.[28]
- The fentanyl transdermal matrix patch was rated by 91% of patients and 93% of physicians in the pilot study as 'equal' to or 'better' than the fentanyl transdermal reservoir patch, with 91% of patients stating a preference for continued therapy with the fentanyl transdermal matrix patch.[28]

5. Dosage and Administration

The fentanyl transdermal matrix patch is indicated in Japan for the management of moderate to severe cancer-related pain in adult patients.[8]

Fentanyl transdermal matrix patches consist of 2.1 mg (surface area 5.25 cm^2), 4.2 mg (10.5 cm^2), 8.4 mg (21.0 cm^2), 12.6 mg (31.5 cm^2) or 16.8 mg (42.0 cm^2) of fentanyl, with corresponding release rates of 12.5, 25, 50, 75 or 100 μg/hour. Each patch is applied for 72 hours; the fentanyl dosage should be individualized until analgesic efficacy is achieved.[8]

The fentanyl transdermal matrix patch is recommended for use in adult patients who are currently receiving opioid therapy, with the initial dose derived from the daily opioid analgesic requirement; dosage conversion schemes (from daily opioid doses) are described in the manufacturer's prescribing information.[8] Additional or alternative analgesia is recommended if the required dosage of the fentanyl transdermal matrix patch exceeds 50.4 mg (300 μg/h) of fentanyl.[8]

The patch is applied to a flat surface of non-irradiated, non-irritated, non-hairy, dry skin on the upper arm, torso or thigh.[8] Any cleaning of the skin should be done with water only.[8] Once the protective layer is removed, the patch should be pressed firmly against the skin, using the palm of the hand, for ≈30 seconds, ensuring complete contact, especially around the edges.[8] After removal of the patch 72 hours later, a new patch should be applied to a different skin site.[8]

Local prescribing information should be consulted for detailed information, including contraindications, drug interactions, precautions and use in special patient populations.

6. Fentanyl Transdermal Matrix Patch: Current Status

The fentanyl transdermal matrix patch is approved in Japan for the management of moderate to severe cancer-related pain in adult patients.[8] It is also indicated in various countries worldwide for the

management of cancer- or non-cancer-related chronic pain.

The efficacy of the fentanyl transdermal matrix patch in managing cancer-related pain was demonstrated in a noncomparative, multicentre, phase II study, with supporting data available from an earlier pilot study in patients with cancer- or non-cancer-related chronic pain. Furthermore, given the nature of the therapy, the tolerability profile of the fentanyl transdermal matrix patch was generally acceptable.

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