

## Transdermal Therapeutic Fentanyl-System (TTS-F)

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**Abstract.** Fentanyl, a surgical analgesic and general anaesthetic, is a lipophilic short-acting synthetic opioid, having a selective potent effect on mu receptors. The transdermal therapeutic fentanyl-system (TTS-F) allows for a continued and sustained titratable amount of fentanyl to be delivered without the inconvenience of the typical 24-h administration of other analgesics. Although incidences of respiratory depression led to TTS-F being contraindicated for postoperative analgesia, it is currently undergoing Phase III trials for nociceptive, neuropathic and chronic moderate to severe pain in a variety of settings. It demonstrates a slow pharmacokinetic profile and incidences of breakthrough pain may still require rapid analgesia, for which intravenous and bolus administration of rapid acting opioids remain 'gold standard'. However, TTS-F is finding uses for chronic pain of cancer origin where it offers a solution for step 3-pain (WHO) management on the WHO analgesic ladder. More recent data indicates that TTS-F is not only effective for neuropathic but also nociceptive non-cancer and cancer pain alike. This review presents an overview of the synthesis, delivery, pharmacokinetics, toxicity and clinical pharmacology of the transdermal delivery of fentanyl.

### Background

The literature from 1987 to date was searched via various databases for titles and abstracts containing the term "Therapeutic Transdermal System-Fentanyl". The authors

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limited this review to articles claiming or appearing to be original research articles. These articles were read *in extenso*.

A reluctance to prescribe strong opioids for the management of chronic pain (especially non-cancer pain), due to concerns about side-effects, physical tolerance, withdrawal and addiction, has prompted the generation of synthetic opioids. Opioids remain the cornerstone of pharmacotherapy for pain, with morphine long being the 'gold standard' for cancer-associated pain. Pain severity, coexisting disease and response to previous therapy, pharmacokinetic profile and available formulations influence the choice of opioid. Short-lived drugs are generally favored since they are easier to titrate than those with a long half-life. Fentanyl is a potent short-acting synthetic pure opiate with a selective activity on mu receptors; it is used as a surgical analgesic and anesthetic. The transdermal therapeutic fentanyl-system (TTS-F) is a long acting controlled-release opioid preparation that limits the inconvenience of 24-h administration of other drugs (1). It is currently in Phase III trials for nociceptive (*i.e.* diabetic ulcer, osteoporotic vertebral fracture, ankylosing spondylitis) and neuropathic pain with or without a nociceptive component (*i.e.* herpetic neuralgia), breakthrough pain and chronic moderate to severe cancer pain (2). The amount of fentanyl released from the TTS is proportional to the surface area; four different sizes are available (25, 50, 75 and 100 µg /h (at 2.5 µg/cm<sup>2</sup>/h)). After the first application of a TTS-F, a fentanyl depot concentrates in the upper skin layer where it takes several hours before clinical effectiveness is reached (3). The time of application to minimal effective and maximum serum concentrations are approximately 2 h and 12 to 48 h, respectively (3, 4). Full clinical efficacy is generally obtained in 8 to 16 h. A steady state level is reached by 72 h, and this is maintained with continued replacement of the patches, once every three days (4-6). Within each 72-h period the serum concentration slowly decreases and, when the patch is

removed, the subcutaneous depot allows for prolonged absorption into the systemic circulation with a terminal half-life of 13 to 25 h. The success of the patch can be attributed to fentanyl's low molecular weight and its highly lipophilic nature (7).

## Synthesis and Delivery

The optimal route of administration of opioids is oral, however, bowel obstruction, severe emesis, coma or dysphagia may preclude this route. Subcutaneous, intranasal, epidural, rectal and transdermal routes provide alternatives (8).

Fentanyl (N-phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide (Mw, 336.5)) is a potent (50-100 times as potent as morphine) highly lipid-soluble, low-molecular weight, short-acting synthetic pure opiate with a selective activity on mu receptors expressed in the brain, spinal cord and other tissues (9). These properties favor transdermal fentanyl administration, which has been characterized by simple and comfortable administration of the drug that produces stable plasma concentrations. Fentanyl is principally metabolized by the cytochrome P450 3A4 isoenzyme system *via* oxidative N-dealkylation to norfentanyl and other inactive metabolites.

Transdermal administration of fentanyl is mediated through incorporation into the TTS, consisting of a backing layer of polyester film that seals and protects the drug reservoir. The reservoir contains fentanyl in alcohol and hydroxyethyl cellulose. A rate-limiting ethylene-vinyl acetate copolymer membrane provides constant release of the opioid directly into the skin, where a depot forms in the upper layers. Fick's first law of diffusion approximates the rate of release. A fentanyl containing silicone adhesive is used for maintaining the patch on the skin (10, 11). The TTS has a defined period of onset, followed by a steady state plateau and a declining phase, typifying all such delivery mediators. There are a variety of other similar transdermal delivery systems available including those for nitroglycerine (glyceryl trinitrate), 17-beta-estradiol, clonidine, nicotine, scopolamine (hyoscine) and estradiol/norethisterone acetate, while many others are being developed (12, 13).

Alternative delivery modes for fentanyl include iontophoresis and electroporation (14, 15), ultrasound (16), and continuous subcutaneous infusion (17). The transmucosal route is also being investigated for other members of the fentanyl series including alfentanil (displaying the most rapid analgesic onset, time to peak effect, shortest distribution and elimination), remifentanyl, sufentanyl, and also for buprenorphine and methadone (18, 19). The oral transmucosal form of fentanyl citrate currently being investigated in clinical trials may be able to provide appropriate control of breakthrough pain (8, 20, 21). Transdermal administration of lidocaine and prilocaine in a format similar to TTS-F are also

available, however, they only induce local anesthesia of the skin and are not yet systemically effective (22).

Several further fentanyl derivatives are currently being studied for clinical application. These include OHM3507, that has a high affinity for mu receptors ( $IC_{50}=10\text{mM}$ ) with 6- and 176- fold lower affinity for delta and kappa receptors respectively, however, it does not display effective opioid action in non-primates (23). Compound 28 has been shown to be a potent mu agonist with similar potency to alfentanil and more efficacious than mirfentanyl in rhesus monkeys, yet little clinical information is available (24).

## Pharmacokinetics/Dynamics and Metabolism

In a bioequivalence study of TTS-F patches in dogs, the average plasma fentanyl concentration for 24 to 72 h was (mean $\pm$ SD)  $0.7\pm0.2\text{ng/ml}$ ,  $1.4\pm0.5\text{ng/ml}$  and  $1.2\pm0.5\text{ng/ml}$  for 50, 75 and  $100\text{ }\mu\text{g/h}$  patches, respectively. The Area Under the Curve (AUC) was  $46\pm12.2\text{ng/h/ml}$ ,  $80.4\pm38.3\text{ng/h/ml}$  and  $101.2\pm41.4$ , while the elimination half-life was  $3.6\pm1.2\text{h}$ ,  $3.4\pm2.7\text{h}$  and  $2.5\pm2.0\text{h}$ , respectively, indicating calculable bioequivalence (25). In swine plasma, TTS-F peaks within 42 to 48 h with concentrations ranging from 0.38 to  $0.99\text{ng/ml}$  (26). Mean ( $\pm$  SD) serum fentanyl concentrations delivered from TTS-F in cats were 1.56 and  $4.87\text{ ng/ml}$  at 8 and 32 h respectively (27). In goats, peak plasma concentrations ranged from 1.12 to  $16.69\text{ng/ml}$  and time to peak concentration ranged from 8 to 18 h. The terminal elimination half-life was  $5.34 \pm 5.34\text{ h}$  (28).

**Clinical data.** In an evaluation of the repeated dose pharmacokinetics of  $100\text{ }\mu\text{g/h}$  TTS-F in humans, absorption was 47% complete at 24h, 88% complete at 48h and 94% complete at 72 h; steady state serum concentrations were approached by the second dosing. By the fifth dosing the mean ( $\pm$ SD) maximum serum concentration was  $2.6\pm1.3\text{ng/ml}$ , the mean standard concentration time curve (0-72h) was  $116.9\pm59.9$  and the terminal half-life following removal was  $21.9\pm8.9\text{ h}$  (9).

The bioavailability of TTS-F ( $100\text{ }\mu\text{g/h}$ ) in humans was investigated in 8 surgical patients and compared to *i.v.* fentanyl. Following removal of the system after 24 h the terminal half-life was  $17.0\pm2.3\text{ h}$ , considerably longer than  $6.1\pm2.0\text{ h}$  for the *i.v.* The rate of fentanyl absorption for the  $100\text{ }\mu\text{g/h}$  system from 4-8 h through to removal at 24 h was constant, with absorption calculated at  $91.7\pm25.7\text{ }\mu\text{g/h}$ . At the time of removal,  $1.07\pm0.43\text{mg}$  fentanyl remained in the depot and fentanyl bioavailability was found to be  $0.92\pm0.33$  with no evidence of cutaneous metabolism or degradation by the skin's bacterial flora (29).

In 39 patients receiving 100 or  $125\text{ }\mu\text{g/h}$ , the calculated clearance was  $1.05\pm0.38\text{l/min}$ , and was not related to age or weight. Mean serum concentrations were  $1.42\pm0.14$  and

1.90±0.30ng/ml, respectively; time to plateau was 15 h and the elimination half-life 21 h (30). Similarly, in 8 patients following orthopedic surgery, a median time lag of 2.25 h before appearance of fentanyl in the blood and a median peak concentration time to a peak of 1.0ng/ml and 22 h, respectively, were observed (31).

Further analysis across age groups demonstrated the likelihood of increased absorption and/or decreased clearance in the elderly (32); although this will require further investigation, the administration to the elderly, or those with hepatic or renal failure, is not recommended. TTS-F administration in young subjects (19-27 years) indicates a mean plasma concentration of 0.88±0.44ng/ml and an AUC (0-60h) of 21.0±10.4ng.h.ml<sup>-1</sup> compared to elderly subjects (67-87 years) where mean plasma concentrations of 2.05±1.10ng/ml and an AUC (0-60h) of 20.4±10.3ng.h.ml<sup>-1</sup> are observed. The higher serum concentrations ( $p=0.034$ ) reflected increased absorption and/or decreased clearance in the elderly (32). However, another study displayed a mean maximum plasma concentration of 1.9ng/ml (young patients (mean age 32.7)) and 1.5ng/ml (elderly (mean 73.7)) (33). Absorption in children (18-60 months) indicates a time to mean peak (± SD) concentration of 18 h with a maximum concentration of 1.7ng/ml, with an elimination half-life of 14.5 h and an AUC of 86.8 ng.h.ml<sup>-1</sup> (34, 35). Absorption in children (18-60 months) indicated a time to mean peak (± SD) concentration of 18 h with a maximum concentration of 1.7ng/ml, with an elimination half-life of 14.5 hours and an AUC of 86.8ng.h.ml<sup>-1</sup>, indicating potentially similar pharmacokinetics across all age groups (34, 35).

### Toxicity and Contraindications

The therapeutic range of fentanyl is between 1ng/ml to 3ng/ml (36). Overdose can occur if the blood concentration is significantly raised, which may result in respiratory depression/ failure (37-39). Inappropriate use, either accidental or intentional, of fentanyl patches, new or re-used (following the standard 3-day application), have been the cause of fentanyl intoxication and overdose (40-46). Specific events have included *i.v.* administration of patch contents (47), myoclonus secondary to withdrawal (48) and transmucosal absorption (49). Fentanyl is a schedule II controlled substance and can produce drug dependency similar to that of other opioids; overdose may lead to an extension of its pharmacological actions with hypoventilation being a serious significant effect.

The effectiveness of TTS-F was first demonstrated in acute postoperative pain; however, the slow pharmacokinetics and large variability, together with the relatively short duration of postoperative pain, precluded adequate dose finding and led to inadequate pain relief. This, together with a high incidence of respiratory depression, has led to

contraindication as a postoperative analgesic (3, 50). It is contraindicated in patients with decreased respiratory function or when other respiratory depression drugs have been given. Respiratory depression can be reversed by the administration of the specific opioid antagonists naloxone or doxapram. One other contraindication is the time lag before pain relief sets in, thus a concomitant short acting analgesic should be given during the initial titration period (up to 12 h) following application of the first patch (2, 50).

The range of reported side-effects are similar to those for other opioids *i.e.* gastrointestinal and neuropsychological; including sedation, nausea, vomiting and constipation (3, 50). Other more specific side-effects include a variety of skin sensitivity reactions not only fentanyl-associated but also patch-associated (51, 52); fentanyl-associated SIADH has also been reported (syndrome of inappropriate antidiuretic hormone secretion) (53).

### Non-human Clinical Pharmacology

A number of trials are proving that TTS-F is safe and effective in the alleviation of perioperative pain and stress in various species including cats (54), post-operative pain in swine (55), and orthopedic surgery in dogs (56). The challenge for the future development of such therapeutic systems will depend on the drug and the properties of skin that is targeted (57-59). Cats treated with TTS-F displayed better recovery scores, lower sedation and pain scores compared to those treated with butorphanol when undergoing onychectomy (27). Postoperative analgesia in dogs undergoing major orthopedic surgery results in less pain with TTS-F compared to epidural morphine (55). Similarly, after ovariohysterectomy in dogs, TTS-F was as effective as *i.m.* oxymorphone in producing comparable analgesia (60). Another study of postoperative pain alleviation for abdominal surgery in dogs highlighted some of the concerns observed in human studies (61).

### Clinical Development

#### Phase I/II

Dose finding and investigational studies in various pain management settings, including cancer and non-cancer pain, osteoporosis and AIDS-related chronic pain, have indicated that TTS-F requires individualized patient titration in most instances to maintain analgesia. Under these conditions pain is maintained as satisfactory, and generally fewer side-effects are reported than with morphine or other opioid analgesics. Studies have shown long-term maintenance of between 2 and 855 days with dose titrations ranging from 25 µg/h to 350 µg/h coupled with improvements in QOL (62-79).

Table I. *Selected cancer studies.*

Effect studied	Experimental model	Results	Reference
Titration from oral morphine for cancer pain control. Safety and efficacy.	Prospective, open label. Phase II.	All 130 patients were receiving 280-360mg codeine requiring rescue morphine, 5mg every 4-6h for up to 12h permitted. All patients required upward titration, initial dose 25 µg/h, mean dose day 3 45.9 µg/h and mean dose on day 56 was 87.4 µg/h. Mean pain decreased from 5.96 at baseline to 0.83 on day 3, there were no significant Karnofsky scale differences. Overall satisfaction was high. Nine patients discontinued with inadequate pain relief or side-effects. Constipation, nausea and vomiting were most frequent side-effects.	80
Long-term, safety and efficacy.	Prospective, open label. Phase II.	Long-term therapy (mean 158 days, range 15-855) with TTS-F in 51 patients with cancer pain indicated the requirement for the availability of dose titration (mean initial dose 69.5 µg/h, to mean final dose 167.7 µg/h). Pain reduction was maintained as good, no side-effects were reported and the requirement for laxatives was reported as lower than for previously administered morphine.	110
Titration from oral morphine to TTS-F for pain relief.	Open label, prospective, multicentre. Phase II	53 cancer patients were titrated to 25, 50, 75 or 100 µg/h TTS-F and followed for three months. The mean duration of use was 58±32 days, mean daily morphine on last two days of stabilization was 189±20mg, mean initial TTS-F was 58±6 µg/h, mean breakthrough morphine dose 35mg, mean final TTS-F dose 169±29 µg/h. Pain relief was good to excellent (82%), and 63% preferred TTS-F. Side-effects included nausea (13%), vomiting (8%), skin rash (8%) and drowsiness (4%). There were 17% discontinuations and 30% reported adverse experiences with the patch.	82
TTS-F vs sustained release morphine. Pain-related satisfaction, patient perceived side-effects and well-being.	Cross-sectional QOL. Phase III.	505 cancer pain patients entered. Assessments were made with FACT-G, BPI, MOS and MSAS. Patients on TTS-F were more satisfied with their pain medication ( $p=0.035$ ), experienced lower frequency ( $p<0.002$ ) and impact ( $p<0.001$ ) of side-effects, despite them being older ( $p<0.001$ ) and having lower function of well-being scores ( $p=0.001$ ).	111
TTS-F vs oral morphine. Pain: preference, efficacy and QOL.	Open two period crossover, randomized multicentre. Phase III	202 cancer pain patients. Equality in terms of pain control: WHO and EORTC QOL-G pain assessment. Less constipation ( $p<0.001$ ), drowsiness ( $p=0.015$ ), increased sleep disturbance ( $p=0.004$ ), shorter sleep duration ( $p=0.008$ ) for TTS-F. Patients preferred fentanyl patches to morphine ( $p=0.037$ ).	112
TTS-F in long-term pain management and quality of life	Retrospective, open label, Phase III	1828 cancer pain patients. Transfers from I, II, III steps to TTS-F, and followed for 6 years. Assessments were made with ECOG, QOL, G- BPI, treatment satisfaction and side-effects. 1714 (93.8%) patients were satisfied with their pain medication, while it was correlated with improved quality of life and decreasing pain measures, indicating that TTS-F is effective in overall quality of life besides the pain relief.	113

**Cancer.** Open label and prospective evaluations of efficacy, tolerability and toxicity in cancer pain management have indicated that TTS-F is generally safe and that toxicities were similar to those reported with other opioids. Constipation, nausea and vomiting were the most usual side-effects with data showing that the severity and incidence in constipation (or the requirement for laxatives) was less when compared to morphine (62, 80-83). Pain relief was rated as good in

49% to 82% of patients and as many as 63% of patients showed a preference for TTS-F (82, 83). Titration of TTS-F ranged from 25 µg/h to 225 µg/h over a period of up to 56 days. In a dose finding study with 20 cancer pain patients over a 28-day period, effective pain management was demonstrated with 70, 98, 107 and 116 µg/h TTS-F at weeks 1, 2, 3 and 4, respectively. By day 15 there was no further statistically significant rise in analgesic dose (65). In a series

Table II. *Selected non-cancer studies.*

Effect studied	Experimental model	Results	Reference
Long-term efficacy and side-effects of TTS-F (100 µg/h) post-operatively.	Double blind, placebo-controlled. Phase II.	Recruitment was stopped after enrollment of 24 patients on safety grounds. TTS-F group was more satisfied with pain relief ( $p=0.008$ ), had lower analgesic demand ( $p<0.05$ ) but had a lower respiratory rate ( $p<0.05$ ) and higher level of $\text{tcCO}_2$ ( $p<0.05$ ). Three cases in the TTS-F group experienced bradypnoea ( $<10$ breaths/min), one with heavy sedation, decrease in $\text{PaCO}_2$ (5.8kPa) and increased $\text{PaCO}_2$ (7.5kPa) terminated study. Respiratory depression indicated postoperative use as a contraindication (87), as was indicated in another double blind study in orthopedic surgery (111)	86
Analgesic and respiratory effects of TTS-F (50 and 75 µg/h) post-operatively.	Randomized, double blind, placebo-controlled. Phase II.	In 120 women undergoing abdominal hysterectomy, VAS pain scores were lower for the TTS-F75 and this group required less supplemental morphine. Between 5 and 36h both, TTS-F groups had significantly increased abnormal respiratory patterns including apneic episodes (tidal volume $<100\text{ml}$ x $>15\text{s}$ ) and slow respiratory rate ( $<8$ breaths/min x $>5\text{mins}$ ), requiring oxygen supplementation or opioid reversal with naloxone. 9 patients were withdrawn. No significant group difference for incidence of nausea, vomiting or pruritus was observed.	87
Safety and efficacy. TTS-F (75 µg/h) for 24 h post-operatively.	Randomized, double blind, placebo-controlled. Phase II.	Fewer patients in the fentanyl group of 42 patients undergoing shoulder surgery required less postoperative parental narcotics ( <i>i.e.</i> morphine) while the patch was in place ( $0.8\pm0.61$ vs $1.3\pm0.64\text{mg/h}$ ) and for 12h following patch removal $0.3\pm0.36$ vs $0.5\pm0.32\text{mg/h}$ ). Vomiting was more frequent in the active group (73% vs 30%) and respiratory rate lower ( $14\pm3$ vs $16\pm2$ breaths/min),	92
Long-term effect and efficacy of TTS-F	Prospective, open label study, Phase III.	529 patients with chronic non-cancer patients were evaluated to determine the safety and efficacy of TTS-F. Median duration of the study was 10 months and 474 (90%) patients sustained such efficacy. TTS-F offers increases in QOL-Short Form 12 and Greek BPI ( $p<0.0001$ ). Side-effects were constipation (range 4.6%-23.1%), nausea (range 1.7%-1.8%) and vomiting (0.2%-0.2%). The severity of all other side-effects was manageable.	115
Level of pain control and QOL. TTS-F vs sustained release oral morphine.	Randomized, international, open label crossover trial. Chronic non-cancer pain. Phase III.	Of 212/256 evaluable patients, 138 (65%) preferred TTS-F, 59 (28%) morphine for ease of application. Pain was reported as good or very good for TTS-F compared to morphine (35% vs 23%; $p=0.002$ ). The incidence of adverse events was similar, more constipation with morphine (48% vs 29%, $p<0.001$ ) and 41% experienced mild cutaneous problems with the patch.	114
TTS-F (75 and 100 µg/h) post-operatively	Randomized, placebo-controlled double blind postoperative. Phase III.	In a postoperative pain study of 143 patients receiving placebo, 75 or 100 µg/h TTS-F, analgesia was significantly better ( $p<0.05$ ) in the TTS-F groups, requiring less morphine; however, they experienced greater incidences of respiratory depression than the placebo group.	89
Efficacy of TTS-F vs placebo, post-operative analgesia.	Randomized, placebo-controlled, double blind. Phase III.	A similar study with 81 patients undergoing total abdominal hysterectomy indicated that higher dose delivery of TTS-F was associated with lower visual analogue pain scores and reduced patient controlled analgesic morphine. However, respiratory rate decreases were also associated with higher doses.	116

of 11 cancer pain patients dose escalations from 25 to 325 µg/h were required over a 28-day period to maintain analgesia. No significant adverse reactions to the medication were reported (66). The analgesic efficacy and side-effects of TTS-F

in 16 cancer pain patients indicated that good analgesia was achieved in 69% of patients with a mean initial dose of  $94\pm99$  µg/h and a final dose  $156\pm149$  µg/h, with the most frequent adverse reaction being constipation (10%) (81). An



open label pilot study to define efficacy, acceptability and toxicity of TTS-F (25 or 50 µg/h patches only) in 35 ambulatory cancer pain patients indicated that 49% vs 6% of patients were satisfied with analgesia, a 24-29% reduction in overall pain compared to base line and toxicities were similar to those observed with other opioids (83). In a study where TTS-F was home prescribed to 44 patients with cancer pain and chronic non-malignant pain for between 2 to 384 days, good analgesia (80%) was observed, with titrations from 25 to 300 µg/h. TTS-F was discontinued in 17% of subjects due to intractable nausea, diarrhea, adherence problems or poor analgesia, while other side-effects were similar to conventional opioids (64). In an open label, comparative and randomized study comparing oral controlled-release morphine to TTS-F with 20 patients per group, there were no significant differences in analgesic efficacy or adverse events (84).

**Non-cancer.** In a series of randomised and placebo-controlled studies investigating the efficacy and safety profile of TTS-F in the perioperative setting (*i.e.* orthopedics, hysterectomy, hemorrhoidectomy and urological), it has typically been administered at doses of 70 to 75 µg/h. In nearly all instances patients receiving TTS-F have required less supportive analgesic (usually morphine) and have reported improved pain management with side-effects reported as mild. However, in nearly all studies there has been a significantly increased respiratory pattern including apneic episodes and slow respiratory rates requiring oxygen supplementation, opioid reversal with naloxone and several study discontinuations (85-95). At this point, there was sufficient data from appropriately conducted trials to label postoperative pain as a contraindication.

In a study of 69 subjects with osteoporosis, pain alleviation and QOL improved significantly, and 61% of subjects reported satisfaction with their treatment (96). In a pediatric palliative care population, 23/26 subjects and 25/26 investigators considered TTS-F superior to previous treatment regimens (73). In another pediatric study where TTS-F was administered for up to 112 days, 11/13 patients experienced satisfaction of pain control and improvements in QOL (97).

### Phase III

**Cancer.** There are a number of ongoing Phase III trials in cancer patients investigating not only pain relief and side-effect profile but, more importantly for now, the impact on the patients QOL and also cost-utility analysis with respect to quality adjusted life. At present it appears that TTS-F will find widespread application in this indication; the availability of meta-analysis in the next few years will clarify this. An overview of selected Phase II and III studies in cancer patient populations is shown in Table I.

**Non-cancer.** Following the discovery that postoperative TTS-F is a contraindication for its use, studies have been addressing other indications of pain alleviation. A relatively small open labelled crossover study in pancreatitis patients indicated that it is not recommended as first choice in this indication (98), and a larger controlled study supports this (99). In a randomized, double blind, placebo-controlled study of 62 patients presenting for orthopedic surgery, 50 or 75 µg/h TTS-F was administered showing no significant advantage between the three groups in pain management (85). In 60 patients undergoing knee arthrotomy, patients received either TTS-F (75 µg/h) or placebo. A statistically significant difference in favor of TTS-F was found ( $p < 0.001$ ) for escape medication, while all other parameters were similar with no reported adverse events (93).

Further long-term randomized studies specifically aimed at pain management for nociceptive pain will also need to address patients QOL. An overview of selected non-cancer studies is presented in Table II.

### Economics

A cost-utility analysis of TTS-F (\$2,491), controlled release morphine (\$2,037) and controlled release oxycodone (\$2,307) for one year of therapy indicated an incremental cost-utility ratio for TTS-F of \$20,709 (*vs* morphine) and \$5,273 (*vs* oxycodone) per quality-adjusted life (QAL) year based on QAL days gained (100). Further QAL analysis is required.

### Opioid Rotation and the WHO Ladder

Recently there has been much debate concerning the application of TTS-F to patients with moderate to severe pain, typically of cancer origin, but also of non-malignant pain. Discussions have centered on the appropriateness of overstepping step 2 on the World Health Organizations (WHO) guidelines for the pain management ladder and proceeding directly to step 3. Standard practice in many institutions is what is termed opioid rotation. Reasons for such rotation include inadequate pain relief, patients wish to reduce oral medication, gastrointestinal side-effects such as nausea, vomiting, constipation and many others (101-104).

Concerns about the use of TTS-F, even in the case of moderate to severe chronic pain, is that immediate pain alleviation is not offered by the fentanyl system and rescue opioid for breakthrough pain is required. However, considering that breakthrough pain in all step 3 cases of pain management would require rescue above any given medication once the steady state level of fentanyl is reached, pain control would follow a similar path in both cases. It is the question of appropriate control, administration and monitoring, especially in the dose titration period(s), that currently limits the widespread application of TTS-F in such

settings. There have, in recent years, been a number of large surveys addressing the application and use of TTS-F in chronic cancer and non-cancer pain management. These surveys have indicated that, in select patient populations, opioid naïve chronic moderate to severe pain patients can be safely administered TTS-F (80, 103-106).

Smaller controlled studies have demonstrated that these patients can be effectively treated for their pain using TTS-F if administered by appropriately trained departments that offer patient support and adequate monitoring, especially of dose titrations. Patients can safely transfer from step 2 to step 3, or indeed from other step 3 opioids to TTS-F obtaining efficacy of pain alleviation whether their pain is nociceptive or neuropathic in origin (69, 80, 107). Similar results are being obtained in opioid rotation studies (101, 108, 109).

Additional Phase III multicentre studies will be needed to clarify the possibility of overstepping step 2 on the pain ladder in selected indications, and the level of patient care and monitoring necessary during the titration phase.

## Opinion

Most patients, and more specifically those with underlying disease (such as cancer patients), are generally inappropriately managed for pain and that leads to a poor quality of life. Recent guidelines emphasize the treatment individualization of moderate to severe pain with opioids, therefore identification of the appropriate drug and route of administration are essential in meeting patient needs. Side-effects and inefficient relief typically indicate clinical switching/ rotation of one opioid to another and/ or one route to another. TTS-F provides a safe and effective delivery system for which other such opioids (and other medications) will undoubtedly follow. Trials tailored to indicate QAL and QOL parameters *versus* competitors (such as oral controlled release analgesics, and non- *i.v.*, *i.m* or standard oral analgesics) will lead to improved patient management with regard to pain alleviation and, at the same time, address toxicity and side-effects. TTS-F is proving a versatile opioid analgesic for moderate to severe cancer and non-cancer pain independent of patient characteristics, pain type or previous analgesic treatment.

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