



DURAGESIC TREATMENT OF PAIN

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Summary

Transdermal fentanyl (Duragesic) is a skin patch that delivers fentanyl, a potent synthetic opioid drug that selectively and can completely block mu opiate receptors. Originally approved in 1990 to treat acute and postoperative pain in 1990, transdermal fentanyl is widely used to treat chronic pain in many conditions. The fentanyl dose depends on the size of the patch and can be increased in 25 g/hour increments. Patients who have not been on opioids usually achieve analgesia with 25–50 g/hour while higher doses may be necessary in patients already taking opioids. Fentanyl levels reach effective levels 12–24 hours after applying the patch and remain at therapeutic levels for 72 hours. For patients who are already on opioids, most clinicians give an initial opioid dose and then titrate the analgesic levels over several weeks. The most serious adverse side-effect is respiratory depression. The most common side effect is nausea and vomiting. The drug causes mild constipation, skin reactions, and neuropsychological effects. Supplemental opioids are given for “breakthrough” pain. Recent studies suggest that transdermal fentanyl can be effectively used to treat joint and back pain. Several clinical trials suggest that fentanyl may be effective for some forms of neuropathic pain, particularly those resulting from peripheral nerve injuries. Differences of skin absorption and systemic drug clearance, and temperature may markedly influence drug levels. Sudden stoppage may cause withdrawal reactions but these are usually less severe than withdrawal associated with intravenous or orally administered opioids. Fentanyl has substantial substance abuse potential. The drug is comparable or better than other oral strong opioids in cost-effectiveness.

Introduction

A recent [posting](http://sciwire.com) on the CareCure Forum (<http://sciwire.com>) asked about the use of Duragesic patches to treat neuropathic pain after spinal cord injury. I did a literature research on the subject. Although the evidence of Duragesic effect on neuropathic pain after spinal cord injury is still sparse, much data is available concerning the effects of Duragesic patches on pain. The following is a summary of the literature.

Duragesic is a transdermal patch system that delivers fentanyl (a potent opioid drug) through the skin. Made by Janssen Pharmaceuticals, a company affiliated with [Johnson & Johnson](http://www.jnj.com), a single Duragesic patch will provide 72 hours of pain relief (<http://www.duragesic.com/>). Approved by the FDA in 1991, the Duragesic patch was initially used to treat postoperative pain (Bernstein, 1992; Bernstein & Klausner, 1994; MacKay, 1993) and acutely painful conditions, including pancreatitis (Stevens, et al., 2002). Duragesic patches are widely prescribed for patients with terminal cancer pain (Baumrucker, 1996), particularly those with inadequate pain relief and intolerable gastrointestinal symptoms from oral opioids (Iconomou, et al., 2000; Radbruch, et al., 2001). The World Health Organization (WHO) recommends transdermal fentanyl for stable cancer pain (Laval, et al., 2002).

Fentanyl is a highly selective and potent activator of the mu opioid receptor, capable of full activation of the receptors (Zuurmond, et al., 2002). In general, patient and caregiver evaluation of transdermal fentanyl tend to be more positive than clinical impressions (McNamara, 2002). Patches have a strong placebo effect (Kongsgaard & Poulain, 1998) and seem to evoke less fear of addiction and concern about side effects (Radbruch, et al., 2002) than intravenous or oral medication. In a poll of German physicians, 15% rated transdermal fentanyl as a “weak opioid” or even as a non-opioid medication (Sabatowski, et al., 2001). Some nurses have similar misconceptions (Ferrell & McCaffery, 1997). The notion that transdermal fentanyl is an alternative to “strong opioids” can be found in the medical literature (Ahmedzai, 1997).

Duragesic patches are supposed to deliver a steady-state dose through the skin. The dosage is adjustable in increments of 25 g/hour with larger patches. In patients with cancer pain and who were not taking opioids, transdermal fentanyl in the range of 25–50 g/hour with oral morphine (5–10 mg q4–6h) as “rescue medication” for breakthrough pain, provided adequate pain relief in 84% of cases. The 50, 75, or 100 g/hour doses should be used only in patients who are tolerant to opioid therapy. Fentanyl overdoses can cause life-threatening hypoventilation (Klockgether–Radke, et al., 2002).

Titration Procedures

Blood fentanyl levels rise gradually after patch application over 12–24 hours and then remain stable for about 72 hours. A fentanyl depot develops in upper skin layers and full clinical effects of the drug do not appear for 8–16 hours (Alsaahaf & Stockwell, 2000). After the patch is removed, serum fentanyl concentrations fall by 50% in about 16 hours. Patients who are already on mild or strong opioids should get an initial intravenous dose of fentanyl. The Duragesic patch dose can be increased in 25 µg/hour steps during the first 48 hours until adequate pain relief is achieved with minimal side effects. “Breakthrough” pain can be treated with “rescue” doses of oral morphine.

Elsner, et al. (Elsner, et al., 1999) examined 101 patients who had been switched from other analgesics to transdermal fentanyl. Nearly half of the patients were on slow-release oral morphine, 17% on immediate-release morphine, 11% of buprenorphine, 11% on tramadol, 5% of levomethadone, 5% on tilidine/naloxone, and 3% on piritramid; 33% of the patients switched because of inadequate pain relieve, 20% to reduce oral medication, 31% because of gastrointestinal side effects, 13% due to vomiting, 19% because of constipation, and 27% from dysphagia. Mystakidou, et al. (Mystakidou, et al., 2001) reported successful conversion of patients on codeine to fentanyl for cancer pain control.

Korte, et al. (Korte, et al., 1996) assessed titration procedures for Duragesic patches in 39 patients. The patch reduced pain after 24 hours and produced satisfactory analgesia within 48 hours. Nearly half of the patients required early increases in dosing. Significant dose increases were necessary during weeks 1–4 to maintain pain control. While Duragesic produced the usual opioids side effects of opioids, side effects such as constipation were less than systemic fentanyl injections. They recommended an initial dose of intravenous fentanyl, placing the Duragesic patch, closely monitoring the patients during the 48 hours, and continued dose adjustment for four weeks. Transition from intravenous to transdermal fentanyl can be done with a 1:1 intravenous:transdermal conversion ratio (Kornick, et al., 2001).

Breitbart, et al. (2000) suggested that manufacturer recommended equi-analgesic doses of transdermal fentanyl are low, resulting in inadequate initial doses and overlong titration periods. However, once switched over, patients are more satisfied with Duragesic patches than with oral morphine. Payne, et al. (Payne, et al., 1998) assessed 504 patients with advanced cancer and showed that they were more satisfied overall with Duragesic patches than other forms of opioids.

Side Effects

The most serious adverse side-effect of transdermal fentanyl is depressed breathing or hypoventilation in about 2% of the patients (Muijsers & Wagstaff, 2001). In some cases, patches were misapplied. For example, placing a transdermal fentanyl patch to mucosal membrane (Kramer & Tawney, 1998), inadvertent use of multiple patches, increased fentanyl absorption due to high temperatures (Frolich, et al., 2001), or intravenous administration of a fentanyl patch content (Reeves & Ginifer, 2002) can cause fatal overdoses.

The most frequent side effects are nausea and vomiting. In one study (Woodroffe & Hays, 1997), 17% of patients withdrew from the study due to unacceptable side-effects including intractable nausea, diarrhea, adherence, or poor analgesia. Sloan, et al. (Sloan, et al., 1998) reported 30% of patients receiving transdermal fentanyl had adverse experiences, including nausea 13%, vomiting 8%, skin rash 8%, and drowsiness 4%; 17% withdrew from the study. Nausea and vomiting can be managed with anti-emetic treatments (Mantovani, et al., 1999). Allan, et al. (Allan, et al., 2001) compared transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain; only 10% of the transdermal fentanyl group withdrew due to intolerable side-effects.

Other side effects include constipation, skin reactions, and neuropsychological effects. Transdermal fentanyl causes less constipation than sustained-release oral morphine (Ahmedzai & Brooks, 1997). In one study (Vielvoye-Kerkmeer, et al., 2000), only 11% of patients complained of constipation. Skin reactions occur in 1–3% of patients, including erythema, papules, itching, and edema. Rotating the patch site (Murphy & Carmichael, 2000) and topical corticosteroids reduce these skin problems. Neuropsychological side effects of opioid therapy decline after several weeks of therapy. Although transdermal fentanyl reduced attention, reaction, visual orientation, motor coordination, and vigilance, it did not impair psychomotor or cognitive performance enough to prevent driving (Sabatowski, et al., 2003).

The side-effects of transdermal fentanyl in children appear to similar to those in adults (Collins, et al., 1999; Paut, et al., 2000). Noyes & Irving (Noyes & Irving, 2001) treated 13 children ranging from 3.75 to 18 years and who had been receiving oral morphine; 11 expressed satisfaction with pain relief and quality of life. Hunt, et al. (Hunt, et al., 2001) converted 41 children from oral morphine (median dose 60 mg/day) to transdermal fentanyl (25 g/hour). After 15 days, the median fentanyl dose was 75 g/hour (range 25–250 g/hour) with no serious adverse events.

Supplemental Opioids

In patients with severe pain, additional oral opioid drugs are usually prescribed for “breakthrough pain”, i.e. rescue dosing. In a retrospective analysis of in-patient notes of 278 hospice patients, Lawrie, et al. (Lawrie, et al., 2003) found that 20% were using transdermal fentanyl and 62% of those had additional strong opioid analgesic prescriptions for breakthrough pain. Another survey (Robards, 2001) of 25 patients receiving transdermal fentanyl indicated that they took a mean of 6.1 ± 0.7 doses of “rescue” opioid per day (range of 0–12 doses per day). Such cases suggest that inadequate transdermal fentanyl dosing may be common. Well titrated patients (Nugent, et al., 2001) required fewer “rescue doses” than other drugs, for example, subcutaneous infusion of diamorphine (Ellershaw, et al., 2002).

A promising new “rescue drug” is transmucosal fentanyl citrate (OTFC) to treat “breakthrough pain” (Farrar, et al., 1998). Christie, et al., (Christie, et al., 1998) showed that a single-unit dose of OTFC can safely, rapidly, and effectively treat breakthrough pain in patients on transdermal fentanyl. Coluzzi, et al. (Coluzzi, et al., 2001) did a double-blind, double-dummy, randomized, multicenter, crossover comparison of OTFC and morphine sulfate immediate release (MSIR) in patients taking transdermal fentanyl. Of 134 patients, 69% found a dose of OTFC that provided more effective pain relief than MSIR. More patients preferred OTFC to MSIR. The combination of transmucosal and transdermal fentanyl will further expand use of this analgesic (Payne, 1998).

The use of additional opioids may contribute to the side effects of transdermal fentanyl. According to Menten, et al. (Menten, et al., 2002) who studied 663 patients that had Duragesic patches delivering 25–950 g/hour of drug, 40% of the patients reported constipation. The constipation depended on the rescue dose of morphine used and did not correlate with transdermal fentanyl dose. Patient acceptance of the Duragesic patches was high with 85% of patients rating convenience as good to excellent. In older patients, there was a slight increased in non-serious adverse events but otherwise similar ease of use and tolerance.

Asians, perhaps because 17–25% of them have deficiencies of enzymes that metabolize proton pump inhibitors (Chong & Ensom, 2003), may have different drug half-lives (Goldstein, 2001; Lotsch, et al., 2002). In one study (Yeo, et al., 1997), 57% of Chinese patients withdrew from transdermal fentanyl treatment due to side-effects or titration difficulties. Although alfentanil doses required for analgesia were similar in Asians and Europeans, Asians have slower recovery times (Aun, et al., 1988). Supplemental opioids should be given with care in Asians.

Indications for Transdermal Fentanyl

The original indication for transdermal fentanyl analgesia was acute pain and postoperative pain (Fiset, et al., 1995). However, due to the slow onset of drug levels from the transdermal delivery and 3-day maintenance of drug levels, the system was clearly more suited for treatment of chronic pain conditions. By 1998, the World Health Organization (WHO) recommended transdermal fentanyl for treatment of stable cancer pain (Radbruch, et al., 1999). Transdermal fentanyl is often used as a replacement therapy for other forms of parenteral opioids, as well as spinal opioids (Enting, et al., 2002). Despite many positive trials indicating patient satisfaction with transdermal fentanyl, many physicians are still reluctant to initiate transdermal fentanyl in patients who do not have terminal disease. However, a growing body of literature supports use of transdermal fentanyl therapy for chronic non-cancer pain.

Transdermal fentanyl has been used to treat rheumatologic pain. Grilo, et al. (Grilo, et al., 2002), for example, treated 67 patients with low back pain and sciatica, inflammatory arthritis, brachial neuralgia, osteoarthritis, and other types of rheumatic pain. In most cases, the transdermal fentanyl was used to replace oral hydromorphone that was ineffective or have intolerable side effects. Other studies (Babic-Naglic, et al., 2002) similarly suggested that Duragesic patches resulted in satisfactory long-term pain relief in rheumatic disease and produces only transitory adverse events compared to other opioid regimens.

Transdermal fentanyl also appears to be effective in patients with severe back pain. Ringe, et al. (Ringe, et al., 2002) used transdermal fentanyl to treat 64 patients with back pain due to vertebral osteoporosis and found that 12 had to withdraw, mostly due to nausea, vomiting or dizziness. The remainder had significant reductions in pain and improved quality of life. Strumpf, et al. (Strumpf, et al., 2001) reviewed the literature and concluded that, despite the lack of randomized controlled clinical trials and physician concern about effectiveness and adverse effects of opioids, there is a role of sustained release opioids or transdermal fentanyl in treatment of back pain. Simpson, et al. (Simpson, et al., 1997) used transdermal fentanyl to treat chronic low back pain and showed significant improvement in pain and disability scores with only mild side effects.

Neuropathic Pain

Experience with transdermal fentanyl to treat central neuropathic pain is mixed. DelleMijn, et al. (DelleMijn, 2001; DelleMijn, et al., 1998) gave transdermal fentanyl to patients with a variety of “neuropathic pain” including diabetic ulcer, osteoporotic vertebral fracture, ankylosing spondylitis, herniated disc and herpetic neuralgia. Of 48 patients, 18 (38%) withdrew because of insufficient pain relief. In the remaining 30 patients, 13 (27%) had substantial pain relief and 5 (10%) had moderate relief over 12 weeks. One study (Bleeker, et al., 2001) gave up to 3400 g/hour transdermal fentanyl resulting in plasma levels of 173 ng/ml without relieving central neuropathic pain in a 58-year old woman. Epidural infusion of bupivacaine, however, eliminated the pain.

Several clinical trials assessed intravenous fentanyl (alfentanil) effects on neuropathic pain after central nervous system injuries. Eide, et al. (Eide, et al., 1995) randomized 9 patients with central dysesthesia after spinal cord injury to intravenous ketamine (6 g/kg/min) or alfentanil (0.6 g/kg/min). Both drugs reduce continuous and intermittent neuropathic pain. Ketamine produced bothersome dizziness in one patient and alfentanil produced only modest side effects. DelleMijn & Vanneste (DelleMijn & Vanneste, 1997) randomized 53 patients with neuropathic pain to fentanyl, fentanyl+diazepam, diazepam, or saline. Fentanyl relieved pain better than diazepam or saline. In a study of persistent pain after low back surgery, Sorenson, et al. (Sorensen & Bengtsson, 1997) classified patients into nociceptive pain (n=7), neuropathic pain (n=22), and mixed pain (n=8); 23 of 37 patients responded to intravenous fentanyl and local anesthetic injections, 3 responded to placebo, and none to the alpha receptor blocker phentolamine.

Several trials have shown that fentanyl effectively reduces peripheral neuropathic pain. Jorum, et al. (Jorum, et al., 2003) gave intravenous ketamine or alfentanil to 12 patients with post-traumatic or post-herpetic neuralgia. Both drugs markedly reduced hyperalgesia responses to cold stimuli without altering cold detection thresholds. Likewise, Leung, et al. (Leung, et al., 2001) showed that both alfentanil and ketamine infusions reduced hyperalgesia and cold pain thresholds in patients after peripheral nerve injuries. Pandey, et al. (Pandey, et al., 2002) randomized patients with Guillian-Barre syndrome to gabapentin (Neurontin) and placebo, allowing the patients to take alfentanil for breakthrough pain. The patients used much less fentanyl (i.e. 65 ± 17 g) during gabapentin than placebo (i.e. 211 ± 21 g) phases.

Transdermal Delivery

Not all transdermal fentanyl patches are the same. For example, Fiset, et al. (Fiset, et al., 1995) assessed the pharmacokinetics of a fentanyl patch made by Cygnus in 15 male post-surgical patients. The patients all received 650–750 micrograms (µg) of fentanyl intravenously during anesthesia induction followed by the patch on the upper torso. Fentanyl plasma measurements suggested $63 \pm 35\%$ drug bioavailability. Drug absorption rates ranged from 10 to 230 µg/hour. In 3 subjects, high absorption rates resulted in toxic drug levels, requiring removal of the device. The Cygnus patch was not recommended for postoperative analgesia because of the variability of absorption.

Electrical currents can be used to increase transdermal fentanyl delivery (Conjeevaram, et al., 2002; Gupta, et al., 1999; Vanbever & Preat, 1999). Drug delivery is a function of total current (Gupta, et al., 1998a). Likewise, low-frequency ultrasound (20 KHz) facilitates drug penetration through skin (Boucaud, et al., 2001). These approaches are likely to allow transdermal delivery of other opioids (Grond, et al., 2000). While current induced transdermal fentanyl absorption is not fast as intravenously administered fentanyl, plasma levels and clearance rates are similar for the two routes (Gupta, et al., 1998b). Transdermal electroporation with high voltage pulses (Vanbever & Preat, 1999) can achieve one third maximal fentanyl plasma concentrations of 30 ng/ml within 5 minutes and peak levels in 30 minutes (Vanbever, et al., 1998). Likewise, the finding that heating of the patch increases absorption may be useful for modifying drug delivery (Carter, 2003; Newshan, 1998; Roth, 2002). The ability to modify delivery rates may be useful for titration of doses.

The thickness of skin and subcutaneous fat depots influence absorption and clearance of the transdermally delivered fentanyl. Although the pharmacokinetics of transdermal fentanyl is said to be similar in children, several studies suggest that absorption rates are higher in young people. One study (Mannerkoski, et al., 2001) reported that pain relief was best in children during the first two days but not the third day of the patch. Thompson, et al. (Thompson, et al., 1998) reported that the mean half-time for plasma concentration to double is 4.2 hours in young adults (mean 32 years) compared to 11.1 hours in elderly adults (mean 74 years). Thus, differences of skin thickness, subcutaneous fat, and systemic drug clearance rates related to age, sex, and patch placement may account for significant variability of drug levels in patients treated with transdermal fentanyl.

Toxicity

Toxicity due to fentanyl overdoses is common. Henderson, et al. (Henderson, 1991) studied 112 deaths associated with fentanyl and its analogs in California, concluding that the general availability of the drug may be responsible for the high incidence of overdoses. Roberge, et al. (Roberge, et al., 2000) identified 61 cases of transdermal drug overdoses in a Regional Poison Information System over 5 years, associated with a significant number of hospital admissions. The Los Angeles County Coroner's office (Anderson & Muto, 2000) reported 25 people who died with transdermal fentanyl patches attached at the time of death, i.e. in 15 accidents, 5 natural deaths, 3 suicides, and 2 deaths of undetermined causes. Tissue fentanyl levels were variable ranging from 2–139 g/kg.

One oft-overlooked cause of opioid toxicity is withdrawal symptoms (Parran & Pederson, 2002). Nausea, vomiting, diarrhea, insomnia, and runny noses are the most frequently reported symptoms associated with fentanyl withdrawal. Myoclonus is also a common adverse effect of opioid withdrawal (Han, et al., 2002). However, because transdermally administered fentanyl has a long half-life, withdrawal symptoms are less common with transdermal fentanyl patches than with intravenous or orally administered opioids (Adriaensen, et al., 2003).

Fentanyl has substantial abuse potential (Arvanitis & Satonik, 2002; Reeves & Ginifer, 2002). It is the most commonly abused controlled substance amongst anesthesiologists (Booth, et al., 2002). Because the patches are so convenient, they have substantial potential for misuse (Klockgether-Radke, et al., 2002; Kramer & Tawney, 1998; Purucker & Swann, 2000; Reeves & Ginifer, 2002). Although seldom considered, because fentanyl gets across skin, caregiver toxicity also can occur (Gardner-Nix, 2001).

Increased ambient temperature may be associated with higher fentanyl absorption (Carter, 2003). Warming blankets should not be placed over transdermal medication patches (Roth, 2002). Frolich, et al. (Frolich, et al., 2001) reported a narcotic overdose in a patient that was being rewarmed after surgery. The increase in absorption may account for other heat-related toxicity associated with transdermal fentanyl (Newshan, 1998). Likewise, a patch that is cut apart and placed on patients can lead to serious overdoses (Klockgether-Radke & Hildebrandt, 1997).

Efficacy–Cost Analyses

An efficacy–cost comparison (Neighbors, et al., 2001) of Duragesic, morphine and oxycodone suggested that Duragesic yielded 244 “quality-adjusted life days”, compared to 236 for morphine and 231 for oxycodone. Duragesic patches were slightly more costly during the first year of therapy (\$2491), moderately higher than oral controlled-release morphine (\$2,037) or oral controlled-release oxycodone (\$2,307). However, when compared against other parenteral delivery methods required when patients cannot take oral medications, the cost of transdermal fentanyl is substantially lower than parental opioids.

Table 1 summarizes the consumer costs for common analgesic medication in 2000. The cost of 5 Duragesic patches was \$107.59–\$169.35 compared to \$111.10–\$207.10 per 100 doses of Morphine sulfate (MS Contin) and \$237.35 for Oxycodone HCl (Oxycontin). Since each patch is good for about 72 hours, five patches would be equivalent to 2 weeks usage. Likewise, 100 doses of MS Contin should be sufficient for 20 days. Note also that lower administration costs and easier home use of Duragesic offsets higher purchase costs (Woodroffe & Hays, 1997).

Table 1. Consumer cost of analgesics and adjuvants (2000)

Medication	Size	Cost (US)
Non–Opioids		
Ibuprofen, 200 mg**	100	\$9.05
Ibuprofen, 400 mg	100	\$21.80
Weak Opioids		
Acetaminophen with codeine (300/30)	100	\$22.70
Tylenol with codeine (No. 3)	100	\$22.70
Oxycodone HCl (Oxycontin), 20 mg	100	\$237.35
Codeine sulfate (generic), 30 mg	100	\$52.25
Strong Opioids		
Morphine sulfate (MSIR), 15 mg	100	\$24.09
Morphine sulfate (MSIR), 30 mg	100	\$37.95
Morphine sulfate (MS Contin), 15 mg	100	\$111.10
Morphine sulfate (MS Contin), 30 mg	100	\$207.10
Hydromorphone HCl (Dilaudid), 2 mg	100	\$55.30
Fentanyl (Duragesic–50)	5*	\$107.59
Fentanyl (Duragesic–75)	5*	\$169.35
Methadone HCl (generic), 10 mg	100	\$46.10

*Each patch is good for 72 hours; 5 patches should cover two weeks.

http://www.postgradmed.com/issues/2000/03_00/hartmann.htm

References Cited

- Adriaensen H, Vissers K, Noorduyn H and Meert T (2003). Opioid tolerance and dependence: an inevitable consequence of chronic treatment? *Acta Anaesthesiol Belg* **54**:37–47. Summary: Although opioids provide effective analgesia, largely unsubstantiated concerns about opioid-induced tolerance, physical dependence and addiction have limited their appropriate use. As a consequence, many patients receive inadequate treatment for both malignant and non-malignant pain. However, it has been shown that analgesic tolerance develops less frequently during chronic opioid administration in a clinical context than in animal experiments, and that instituting an appropriate dosing regimen can minimise withdrawal symptoms. Early studies had suggested that addiction might result from chronic opioid therapy, though more recent data indicate a low risk in patients with no history of drug abuse. New treatment regimens may also reduce the risk of tolerance, physical dependence and addiction. Long-acting preparations, such as transdermal fentanyl and possibly some forms of other slow release opioids, which maintain constant opioid concentrations in the plasma, minimise the occurrence of the 'between-dose' symptoms such as withdrawal and opioid-induced euphoria. This review discusses the development of tolerance, physical dependence and addiction during opioid therapy, and the influence of these factors on the choice of treatment. Department of Anesthesiology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium. Hugo.Adriaensen@uza.be
- Ahmedzai S (1997). Current strategies for pain control. *Ann Oncol* **8 Suppl 3**:S21–4. Summary: Pain is the most feared symptom for patients diagnosed with cancer. Although our understanding of cancer pain and its management has greatly improved in the past decade, an unacceptably large proportion of patients still do not receive adequate pain relief. Before commencing any form of treatment, patients must receive a thorough assessment in order to define the pain, causes and severity. The recommendations for progressing a patient from step 2 to step 3 of the WHO analgesic ladder are discussed here as well as the choice of strong opioid substitution. An overview of the benefits of considering alternative routes of administering strong opioids, such as the transdermal delivery of fentanyl (TTS fentanyl), and the use of opioid substitution in patients intolerant to the adverse effects of morphine are also included. Finally, newer approaches to relieving refractory pain, such as neuropathic and bone pain, are considered. Department of Surgical and Anaesthetic Sciences, Royal Hallamshire Hospital, Sheffield, UK.
- Ahmedzai S and Brooks D (1997). Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and

quality of life. The TTS–Fentanyl Comparative Trial Group. *J Pain Symptom Manage* 13:254–61. Summary: Cancer patients requiring strong opioid analgesia (n = 202; mean age, 61.5 years; range, 18–89 years; 55% men) were recruited from 38 United Kingdom palliative care centers into a randomized, open, two–period, crossover study comparing transdermal fentanyl with sustained–release oral morphine. Patients received one treatment for 15 days followed immediately by the other for 15 days. Daily diaries were completed. Both treatments appeared equally effective in terms of pain control, as assessed by the Memorial Pain Assessment Card and European Organization for Research and Treatment of Cancer (EORTC) pain scores. Fentanyl was associated with significantly less constipation ($p < 0.001$) and less daytime drowsiness ($p = 0.015$) but greater sleep disturbance ($p = 0.004$) and shorter sleep duration ($p = 0.008$) than morphine. The World Health Organization (WHO) performance status and EORTC global quality of life scores showed no significant difference between treatment groups. Of those patients who were able to express a preference (n = 136), significantly more preferred the fentanyl patches ($p = 0.037$). We conclude that, in this study, transdermal fentanyl provided pain relief that was acceptable to cancer patients and was associated with less constipation and sedation than morphine. These reduced side effects may contribute to patients preference for the patches. Department of Palliative Medicine, University of Sheffield, Royal Hallamshire Hospital, United Kingdom.

- Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R and Kalso E (2001). Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non–cancer pain. *Bmj* 322:1154–8. Summary: OBJECTIVES: To compare patients' preference for transdermal fentanyl or sustained release oral morphine, their level of pain control, and their quality of life after treatment. DESIGN: Randomised, multicentre, international, open label, crossover trial. SETTING: 35 centres in Belgium, Canada, Denmark, Finland, the United Kingdom, the Netherlands, and South Africa. PARTICIPANTS: 256 patients (aged 26–82 years) with chronic non–cancer pain who had been treated with opioids. MAIN OUTCOME MEASURES: Patients' preference for transdermal fentanyl or sustained release oral morphine, pain control, quality of life, and safety assessments. Results: Of 212 patients, 138 (65%) preferred transdermal fentanyl, whereas 59 (28%) preferred sustained release oral morphine and 15 (7%) expressed no preference. Better pain relief was the main reason for preference for fentanyl given by 35% of patients. More patients considered pain control as being "good" or "very good" with fentanyl than with morphine (35% v 23%, $P=0.002$). These results were reflected in both patients' and investigators' opinions on the global efficacy of transdermal fentanyl. Patients receiving fentanyl had on average higher quality of life scores than those receiving

morphine. The incidence of adverse events was similar in both treatment groups; however, more patients experienced constipation with morphine than with fentanyl (48% v 29%, $P < 0.001$). Overall, 41% of patients experienced mild or moderate cutaneous problems associated with wearing the transdermal fentanyl patch, and more patients withdrew because of adverse events during treatment with fentanyl than with morphine (10% v 5%). However, within the subgroup of patients naive to both fentanyl and morphine, similar numbers of patients withdrew owing to adverse effects (11% v 10%, respectively). **CONCLUSION:** Transdermal fentanyl was preferred to sustained release oral morphine by patients with chronic non-cancer pain previously treated with opioids. The main reason for preference was better pain relief, achieved with less constipation and an enhanced quality of life. Chronic Pain Services, Northwick Park and St Mark's NHS Trust, Harrow, Middlesex HA1 3UJ.

- Alshahaf MH and Stockwell M (2000). Respiratory failure due to the combined effects of transdermal fentanyl and epidural bupivacaine/diamorphine following radical nephrectomy. *J Pain Symptom Manage* 20:210–3. Summary: The transdermal therapeutic system (TTS) fentanyl has been designed for rate-controlled drug delivery. When the system is applied, a fentanyl depot concentrates in the upper skin layers. Plasma concentrations are not measurable until 2 hours after application, and it takes an 8–16 hr latency period until full clinical fentanyl effects are observed. Following removal, serum fentanyl concentrations decline gradually and fall to about 50% in approximately 16 hours. We report the case of a 77-year-old man with a history of severe arthritis, who was receiving transdermal fentanyl and developed respiratory failure after starting epidural diamorphine/bupivacaine for postoperative pain relief following radical nephrectomy. Anaesthetic Department, St. Helier Hospital NHS Trust, Carshalton, Surrey, United Kingdom.

- Anderson DT and Muto JJ (2000). Duragesic transdermal patch: postmortem tissue distribution of fentanyl in 25 cases. *J Anal Toxicol* 24:627–34. Summary: Fentanyl is a potent, short-acting narcotic analgesic widely used as a surgical anesthetic and for the control of pain when administered in the form of a transdermal patch. The success of the patch can be attributed to fentanyl's low molecular weight and its highly lipophilic nature, which enables it to be readily absorbed through the skin and subsequently distributed throughout the body. Over the past three years, the Los Angeles County Coroner's Toxicology Laboratory has encountered 25 cases involving Duragesic patches (fentanyl), and their postmortem tissue distributions are presented here. The analysis of fentanyl from postmortem specimens (3-mL or g sample size) consisted of an n-butyl chloride basic extraction followed by identification and quantitation on a gas chromatograph-mass spectrometer using the

selected ion monitoring (SIM) mode. The fentanyl ions monitored were m/z 245, 146, and 189 and the internal standard, fentanyl-d₅ ions, were m/z 250, 151, and 194 (quantitation ion underlined). The linear range of the assay was 1.67 microg/L to 500 microg/L with the limit of quantitation and detection of 1.67 microg/L. The postmortem tissue distribution ranges of fentanyl in the 25 fatalities were as follows: heart blood, 1.8–139 microg/L (23 cases); femoral blood, 3.1–43 microg/L (13 cases); vitreous, +<2.0–20 microg/L (4 cases); liver, 5.8–613 microg/kg (22 cases); bile, 3.5–262 microg/L (15 cases); urine, 2.9–895 microg/L (19 cases); gastric, 0–1200 microg total (17 cases); spleen, 7.8–79 microg/kg (3 cases); kidney, 11 microg/kg (1 case); and lung, 31 microg/kg (1 case). The age of the decedents in this study ranged from 19 to 84, with an average age of 46. The modes of death included 15 accidental, 5 natural, 3 suicidal, and 2 undetermined. The main objectives of this paper are to show the prevalence of fentanyl patches in our community and to aid the forensic toxicologist with the interpretation of postmortem fentanyl levels in casework. Los Angeles County Department of Coroner, Los Angeles, California 90033, USA.

- Arvanitis ML and Satonik RC (2002). Transdermal fentanyl abuse and misuse. *Am J Emerg Med* **20**:58–9. Summary:
- Aun C, Houghton IT, Chan K, Carley RH, Salmon NP, Lams YM and Thornton JA (1988). A comparison of alfentanil requirements in European and Asian patients during general anaesthesia. *Anaesth Intensive Care* **16**:396–404. Summary: Alfentanil requirements were compared in thirty-six Asian and forty-three European patients during general anaesthesia with muscle relaxants. Alfentanil infusion at 5 micrograms/kg/min was started immediately after induction with thiopentone and alcuronium. The infusion rate was reduced to 0.5 microgram/kg/min after ten minutes. An incremental dose of 5 micrograms/kg/min for five minutes was given on each occasion when anaesthesia was clinically judged to be inadequate. Recovery parameters were recorded. Pharmacokinetics were also studied in five Europeans, four Chinese and four Nepalese. The dosage of alfentanil required was comparable in both Asian and European patients, but recovery was slower in the Asian patients. The elimination half-life in the Chinese and the Nepalese were both significantly shorter than that of the Europeans (P less than 0.05), but at the time of recovery of spontaneous ventilation, the mean plasma concentrations were not significantly different. Department of Anaesthesia, Chinese University of Hong Kong.
- Babic–Naglic D, Jajic Z, Gnjjidic Z and Stambuk B (2002). [Treatment of chronic pain--use of transdermal fentanyl (Duragesic TTS)]. *Reumatizam* **49**:33–7. Summary: Incorrect treatment of chronic pain is common cause

of patient's discontentment and suffering. The problem is mostly occurring because of inappropriate pain treatment. The WHO guidelines recommends declining of prejudices and using of strong opioids in therapy after the unsatisfactory treatment with weaker analgesics. Strong opioid analgesic fentanyl in transdermal system (Duragesic TTS) is introduced. In rheumatology, it is recommended for all conditions characterised by chronic pain with intensity 4 and more on the VAS scale (0–10). It is mostly used in rheumatoid arthritis, osteoarthritis, low back pain and neuropathic pain. Duragesic TTS provides continuous pain relief for 72 hours, with constant serum concentrations. It has to be gradually titrated and starting dose is 25 micrograms/h. Possible adverse events (nausea, vomiting, constipation, sedation, itching) are short termed, transitory and easily managed. Results of some clinical trials and personal experiences that are proving its efficacy and safety are presented. Klinika za reumatske bolesti i rehabilitaciju, KBC Zagreb, Zagreb.

- Baumrucker SJ (1996). Duragesic (transdermal fentanyl) in hospice care. *Am J Hosp Palliat Care* **13**:13–5. Summary:
- Bernstein KJ (1992). Comment: Duragesic product labeling. *Ann Pharmacother* **26**:431–2. Summary:
- Bernstein KZ and Klausner MA (1994). Potential dangers related to transdermal fentanyl (Duragesic) when used for postoperative pain. *Dis Colon Rectum* **37**:1339–40. Summary:
- Bleeker CP, Bremer RC, Dongelmans DA, van Dongen RT and Crul BJ (2001). Inefficacy of high-dose transdermal fentanyl in a patient with neuropathic pain, a case report. *Eur J Pain* **5**:325–9; discussion 329–31. Summary: Pain partially responsive to opioids can lead to rapid escalating dosages due to tolerance development. In this report the case of a 58-year-old female with neuropathic pain using increasing transdermal (TTS) fentanyl dosages to a maximum dose of 3400 microg/h resulting in fentanyl plasma levels of 173 ng/ml is described. For pain relief an epidural infusion at the level T1–2 with bupivacaine was started. Immediate pain relief was accompanied by short lasting respiratory depression and drowsiness. Pain Clinic, Department of Anaesthesiology, University Hospital Nijmegen, 6500 HB Nijmegen, the Netherlands.
- Booth JV, Grossman D, Moore J, Lineberger C, Reynolds JD, Reves JG and Sheffield D (2002). Substance abuse among physicians: a survey of academic anesthesiology programs. *Anesth Analg* **95**:1024–30, table of contents. Summary: Efforts to reduce controlled-substance abuse by anesthesiologists have focused on education and tighter regulation of controlled substances. However, the efficacy of these approaches remains

to be determined. Our hypotheses were that the reported incidence of controlled-substance abuse is unchanged from previous reports and that the control and accounting process involved in distribution of operating room drugs has tightened. We focused our survey on anesthesiology programs at American academic medical centers. Surveys were sent to the department chairs of the 133 US anesthesiology training programs accredited at the end of 1997. There was a response rate of 93%. The incidence of known drug abuse was 1.0% among faculty members and 1.6% among residents. Fentanyl was the controlled substance most often abused. The number of hours of formal education regarding drug abuse had increased in 47% of programs. Sixty-three percent of programs surveyed had tightened their methods for dispensing, disposing of, or accounting for controlled substances. The majority of programs (80%) compared the amount of controlled substances dispensed against individual provider usage, whereas only 8% used random urine testing. Sixty-one percent of departmental chairs indicated that they would approve of random urine screens of anesthesia providers. IMPLICATIONS: This survey indicates that the frequency of controlled substance abuse among anesthesiologists has changed little in the past few years, despite an increase in the control and accounting procedures for controlled substances as well as increased mandatory education. Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina 27710, USA. booth006@mc.duke.edu

- Boucaud A, Machet L, Arbeille B, Machet MC, Sournac M, Mavon A, Patat F and Vaillant L (2001). In vitro study of low-frequency ultrasound-enhanced transdermal transport of fentanyl and caffeine across human and hairless rat skin. *Int J Pharm* **228**:69–77. Summary: The effect of low-frequency sonophoresis on fentanyl and caffeine permeation through human and hairless rat skin was studied in vitro. Experiments were performed using 20 kHz ultrasound applied at either continuous or discontinuous mode and with an average intensity of 2.5 W/cm². The results showed that low-frequency ultrasound enhanced the transdermal transport of both fentanyl and caffeine across human and hairless rat skin. This was explained by both increasing flux during sonication and shortening the lag time. Discontinuous mode was found to be more effective in increasing transdermal penetration of fentanyl while transdermal transport of caffeine was enhanced by both continuous and pulsed mode. Histological and electron microscopy studies showed that human and hairless rat skin was unaffected by ultrasound exposure. Further studies will be necessary to determine the relative contribution of ultrasound parameters in low-frequency ultrasound-induced percutaneous enhancement of drug transport. Laboratoire d'Ultrasons Signaux et Instrumentation (EA 2102), School of Medicine, Tours

University, BP 3223, F-37032 Cedex, Tours, France.
boucau_a@med.univ-tours.fr

- Carter KA (2003). Heat-associated increase in transdermal fentanyl absorption. *Am J Health Syst Pharm* **60**:191–2. Summary:
- Chong E and Ensom MH (2003). Pharmacogenetics of the proton pump inhibitors: a systematic review. *Pharmacotherapy* **23**:460–71. Summary: Cytochrome P450 (CYP) 2C19 mediates the major metabolic transformations of the proton pump inhibitors (PPIs) omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole. Genetic polymorphism of CYP2C19 can lead to significant phenotypic variation in the activity of this isoenzyme and thus in the metabolism of PPIs. We systematically reviewed the pharmacogenetic studies of PPIs with respect to the effects of CYP2C19 polymorphism on the clinical outcomes of PPI therapy. We searched MEDLINE (January 1966–August 2002) and EMBASE (January 1988–August 2002) for English-language articles on the pharmacogenetics of PPIs; the search was supplemented by a bibliographic review of all relevant articles. Seventeen pertinent citations were identified, and the quality (level) of evidence for each was categorized according to the rating scale of the United States Preventive Services Task Force. We found that the relationship between CYP2C19 genetic polymorphism and clinical outcomes after PPI therapy has not yet been clearly delineated. Virtually all pharmacogenetic studies of PPIs have been performed in Japanese men; thus, the clinical relevance of CYP2C19 genetic polymorphism in non-Asian patients and women is unknown. Differences among dual- and triple-therapy drug regimens make it difficult to compare H. pylori eradication studies and assess their applicability to current practice patterns. Drug adherence, a pivotal factor in the success of eradication therapy, was addressed in only four trials. Future directions for research include performing more studies with larger sample sizes, particularly in non-Asian populations and women; measuring plasma PPI concentrations to directly correlate H. pylori infection and ulcer cure rates with plasma drug availability; expanding the study population to patients with gastroesophageal reflux disease; and exploring the influence of CYP3A4 in the success or failure of PPI therapy. Although CYP2C19 genotyping is currently only a research instrument, it may be a valuable clinical tool in select patients to ensure optimal PPI therapy. Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada.
- Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E and Portenoy RK (1998). Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in

cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol* **16**:3238–45. Summary: PURPOSE: Supplemental, "as-needed," administration of an opioid is a common approach to the problem of breakthrough pain in cancer patients. Oral transmucosal fentanyl citrate (OTFC) is undergoing investigation as a new treatment for breakthrough pain. The primary purpose of the study was to demonstrate that a single-unit dose of OTFC can safely and effectively treat breakthrough pain. A secondary goal was to determine appropriate dosing guidelines. PATIENTS AND METHODS: This was a multicenter, randomized, double-blind, dose-titration study in 62 adult cancer patients using transdermal fentanyl for persistent pain. Consenting patients provided 2 days of baseline data to evaluate the performance of their usual breakthrough pain medication. Patients then randomly received 200 microg or 400 microg OTFC in double-blind fashion. (Patients were always assigned, rather than randomized, to 200 microg if 400 microg represented > 20% of around-the-clock medication.) Pain intensity (PI), pain relief (PR), and global satisfaction scores were recorded. OTFC was then titrated until the patient received adequate PR for each episode using one OTFC unit. Orders to titrate up were ignored one third of the time to improve the blind. Two days of baseline data were compared with 2 days of OTFC data after titration identified an effective dose of OTFC. RESULTS: Most patients (76%) found a safe and effective dose of OTFC. There was no meaningful relationship between the around-the-clock opioid regimen and the effective dose of OTFC. In open-label comparisons, OTFC produced a faster onset of relief and a greater degree of PR than patients' usual breakthrough medication. Somnolence, nausea, and dizziness were the most common side effects associated with OTFC. CONCLUSION: Most patients find a single OTFC dosage that adequately treats breakthrough pain. The optimal dose is found by titration and is not predicted by around-the-clock dose of opioids. Hospice Institute of Florida Suncoast and University of South Florida, College of Medicine, Department of Anesthesiology, Tampa 33612-4799, USA.

- Collins JJ, Dunkel IJ, Gupta SK, Inturrisi CE, Lapin J, Palmer LN, Weinstein SM and Portenoy RK (1999). Transdermal fentanyl in children with cancer pain: feasibility, tolerability, and pharmacokinetic correlates. *J Pediatr* **134**:319–23. Summary: OBJECTIVES: (1) To assess the feasibility and tolerability of the therapeutic transdermal fentanyl system (TTS-fentanyl) by using a clinical protocol developed for children with cancer pain. (2) To estimate the pediatric pharmacokinetic parameters of TTS-fentanyl. METHODS: The drug was administered in open-label fashion; and measures of analgesia, side effects, and skin changes were obtained for a minimum of 2 doses (6 treatment days). Blood specimens were analyzed for plasma fentanyl concentrations. The pharmacokinetics of TTS-fentanyl were estimated by using a mixed effect modeling approach.

RESULTS: Treatment was well tolerated. Ten of the 11 patients who completed the 2 doses continued treatment with TTS–fentanyl. The duration of treatment ranged from 6 to 275 days. The time to reach peak plasma concentration ranged from 18 hours to >66 hours in patients receiving the 25 microg/h patch. Compared with published pharmacokinetic data from adults, the mean clearance and volume of distribution of transdermal fentanyl were the same, but the variability was less. **CONCLUSIONS:** Treatment of children with TTS–fentanyl is feasible and well tolerated and yields fentanyl pharmacokinetic parameter estimates similar to those for adults. A larger study is required to confirm these findings and further test the clinical protocol. Pain and Palliative Care Service and the Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York, USA.

- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M and Portenoy RK (2001). Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* **91**:123–30. Summary: Oral transmucosal fentanyl citrate (OTFC; Actiq) is a drug delivery formulation used for management of breakthrough cancer pain. Previous studies with open–label comparisons indicated OTFC was more effective than patients' usual opioid for breakthrough pain. The objective of this study was to compare OTFC and morphine sulfate immediate release (MSIR) for management of breakthrough pain in patients receiving a fixed scheduled opioid regimen. This double–blind, double–dummy, randomized, multiple crossover study was conducted at 19 US university– and community–based hospitals and clinics and comprised 134 adult ambulatory cancer patients. Patients were receiving a fixed scheduled opioid regimen equivalent to 60–1000 mg/day oral morphine or 50–300 microg/h transdermal fentanyl, were using a 'successful' MSIR dose (15–60 mg) as defined by entry criteria, and were experiencing 1–4 episodes of breakthrough pain per day. In open–label fashion, OTFC was titrated such that a single unit (200–1600 microg) provided adequate pain relief with acceptable side effects. Successfully titrated patients entered the double–blind phase of the study and received ten prenumbered sets of randomized capsules and oral transmucosal units. Five sets were the successful OTFC dose paired with placebo capsules, and five sets were placebo OTFC paired with capsules containing the successful MSIR dose. Patients took one set of study medication for each episode of target breakthrough pain. Pain intensity (PI), pain relief (PR) and global performance of medication (GP) scores were recorded. Pain intensity differences (PID) were calculated and 15–min PID was the primary efficacy variable. Adverse events were recorded. Sixty–nine percent of patients (93/134) found a successful dose of OTFC. OTFC yielded outcomes (PI,

PID, and PR) at all time points that were significantly better than MSIR. GP also favored OTFC and more patients opted to continue with OTFC than MSIR following the study. Somnolence, nausea, constipation, and dizziness were the most common drug-associated side effects. In conclusion, OTFC was more effective than MSIR in treating breakthrough cancer pain. The Oncology Center at St. Joseph Medical Plaza, 1140 West LaVeta, Suite 450, Orange, CA 92868, USA. phcbcc@aol.com

- Conjeevaram R, Banga AK and Zhang L (2002). Electrically modulated transdermal delivery of fentanyl. *Pharm Res* **19**:440–4. Summary: PURPOSE: Test to determine if iontophoresis and electroporation, alone or in combination, can be used for rapid and modulated delivery of fentanyl. METHODS: Fentanyl citrate (5 mg/ml) dissolved in pH 4.0 citrate buffer was delivered in vitro across human epidermis. For iontophoresis, a current of 0.5 mA/cm² was applied for 5 h, using silver/silver chloride electrodes. Electroporation protocol consisted of applying 15 exponential pulses of 500V (applied voltage) and 200 msec duration at the rate of 1 pulse per minute at time zero and, in some cases, repeating at 1.5 and 2.5 h. RESULTS: There was no measurable permeation of fentanyl through human epidermis under passive conditions. A significant flux (about 80 microg/cm²-hr) was achieved using iontophoresis and decreased once the current was turned off. A 4-fold higher flux and shorter lag time was observed with electroporation as compared to iontophoresis. The flux was found to recover quickly (within 1 h) following pulsing. Modulation of transdermal delivery of fentanyl was demonstrated by both iontophoresis and electroporation. CONCLUSIONS: Electrically assisted transdermal delivery of fentanyl significantly increased transport compared to passive delivery. Also, rapid and modulated delivery was shown to be feasible by programming the electrical parameters. Dept Pharmaceutical Sciences, School of Pharmacy, Mercer University, Atlanta, Georgia 30341, USA.
- DelleMijn PL (2001). Opioids in non-cancer pain: a life-time sentence? *Eur J Pain* **5**:333–9. Summary: There is continuing reluctance to prescribe strong opioids for the management of chronic non-cancer pain due to concerns about side-effects, physical tolerance, withdrawal and addiction. Randomized controlled trials have now provided evidence for the efficacy of opioids against both nociceptive and neuropathic pain. However, there is considerable variability in response rates, possibly depending on the type of pain, the type of opioid and its route of administration, the time to follow-up, compliance and the development of tolerance. Five patients were selected with nociceptive or neuropathic pain in whom other pharmacological or physical therapies had failed to provide satisfactory pain relief. They received transdermal fentanyl (starting dose 25 microg/h) for at least 6 weeks. Transdermal fentanyl dosage was titrated upwards as required. Transdermal fentanyl provided

adequate pain relief in patients with nociceptive pain (diabetic ulcer, osteoporotic vertebral fracture, ankylosing spondylitis) or neuropathic pain with a nociceptive component (radicular pain due to disc protrusion, herpetic neuralgia). The duration of treatment ranged from 6 weeks to 6 months for four cases. In the case of ankylosing spondylitis, treatment was carried out for 2 years, stopped and then restarted successfully. There were no withdrawal effects or addictive behaviour on treatment cessation, regardless of duration of the treatment. In conclusion, strong opioids may provide prolonged effective pain relief in selected patients with nociceptive and neuropathic non-cancer pain. Transdermal fentanyl treatment can often be temporary and can easily be stopped following adequate pain relief without withdrawal effects or any evidence of addictive behaviour. Department of Neurology and Neurophysiology, Saint Joseph Hospital, P.O. Box 7777, 5500 MB Veldhoven, Netherlands. NEI@sjz.nl

- Dellemijn PL, van Duijn H and Vanneste JA (1998). Prolonged treatment with transdermal fentanyl in neuropathic pain. *J Pain Symptom Manage* **16**:220–9. Summary: Forty-eight patients with noncancer neuropathic pain who had participated in a randomized controlled trial with intravenous fentanyl (FENiv) infusions received prolonged transdermal fentanyl (FENtd) in an open prospective study. Pain relief, side effects, tolerance, psychological dependence, mood changes, and quality of life were evaluated. The value of clinical baseline characteristics and the response to FENiv also was evaluated in terms of the outcome with long-term FENtd. Eighteen patients stopped prematurely because of insufficient pain relief, side effects, or both. Among the remaining 30 patients completing the 12-week dose titration protocol, pain relief was substantial in 13 and moderate in five. Quality of life improved (23%, $P < 0.01$). Psychological dependence or the induction of depression was not observed. In only one patient did tolerance emerge. There was a significant positive correlation between the pain relief obtained with FENiv and that with prolonged FENtd ($r = 0.59$, $P < 0.0001$). We conclude that (1) long-term transdermal fentanyl may be effective in noncancer neuropathic pain without clinically significant management problems and (2) A FENiv-test may assist in selecting neuropathic pain patients who might benefit from prolonged treatment with FENtd. Department of Neurology, Saint Lucas Andreas Hospital, Amsterdam, The Netherlands.

- Dellemijn PL and Vanneste JA (1997). Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. *Lancet* **349**:753–8. Summary: BACKGROUND: The effectiveness of opioid analgesics in non-cancer neuropathic pain is unpredictable and can be disappointing. It is not clear whether opioids, when effective, relieve pain by decreasing pain intensity or pain unpleasantness or by

their sedative effect. The aim of this prospective randomised double-blind placebo-controlled crossover trial was to assess relief of pain intensity and pain unpleasantness with intravenous infusions of fentanyl. **METHODS:** We compared the analgesic effect of intravenous dose titration of fentanyl with diazepam (active placebo) or saline (inert placebo) in 53 patients with different types of neuropathic pain. Patients were randomly assigned two consecutive infusions: fentanyl plus diazepam (27 patients) or fentanyl plus saline (26 patients). Study medication was infused at a constant rate for a maximum of 5 h. Pain, sedation, and side-effects were assessed from the start of infusion for 8 h. The primary outcome measure was maximum relief of pain intensity. **FINDINGS:** One patient in the fentanyl/diazepam group and two in the fentanyl/saline group were withdrawn. Maximum relief of pain intensity was better with fentanyl than with diazepam (66% [95% CI 53–80] vs 23% [12–35]) or with saline (50% [36–63] vs 12% [4–20]). The beneficial effect of fentanyl was independent of the type of neuropathic pain and the degree of sedation. Fentanyl therapy produced equal relief of pain intensity and pain unpleasantness, whereas diazepam and saline did not reduce either pain index. Patients reported significantly more side-effects while receiving fentanyl than during diazepam or saline infusion ($p < 0.0001$), but none of the side-effects was severe. **INTERPRETATION:** Fentanyl may relieve non-cancer neuropathic pain by its intrinsic analgesic effect. The clinical characteristics of neuropathic pain do not predict response to opioids. Department of Neurology, Sint Lucas Andreas Ziekenhuis, Amsterdam, Netherlands.

- Eide PK, Stubhaug A and Stenehjem AE (1995). Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. *Neurosurgery* 37:1080–7. Summary: The role of central N-methyl-D-aspartate (NMDA) receptors in the pathogenesis of central pain was examined in nine patients with central dysesthesia pain after spinal cord injury. The central pain syndrome included spontaneous continuous and intermittent pain as well as evoked pain. Pain was evoked by non-noxious stimulation of the skin (allodynia) and by repeated pricking of the skin (wind-up-like pain). The severity of continuous and evoked pain was examined before and after the intravenous infusion of either the NMDA receptor antagonist ketamine (6 micrograms/kg/min after a bolus dose of 60 micrograms/kg), the mu-opioid receptor agonist alfentanil (0.6 microgram/kg/min after a bolus dose of 7 micrograms/kg), or placebo (0.9% NaCl). A randomized, double-blind, crossover study design was used. It was found that both continuous and evoked pain were markedly reduced by the blockade of NMDA receptors by ketamine as well as by the activation of mu-opioid receptors by alfentanil. Neither ketamine nor alfentanil significantly changed thresholds for the sensation of heat pain. The reduction of pain was not

associated with severe side effects; the most severe side effect of ketamine was bothersome dizziness in one patient, and only modest side effects were caused by alfentanil. The present data provide clinical evidence that the development of central dysesthesia pain after traumatic spinal cord injury is dependent on the activation of central NMDA receptors. The results further indicate that mu-opioid receptors are involved in the control of this type of pain. Department of Neurosurgery, Ulleval Hospital, Oslo, Norway.

- Ellershaw JE, Kinder C, Aldridge J, Allison M and Smith JC (2002). Care of the dying: is pain control compromised or enhanced by continuation of the fentanyl transdermal patch in the dying phase? *J Pain Symptom Manage* 24:398–403. Summary: The introduction of fentanyl transdermal patches has led to concern and confusion regarding the management of pain control in the dying phase. Data were collected retrospectively from 94 dying patients. Two groups were identified—patients treated with fentanyl transdermal patch who remained on the patch in the dying phase and patients on oral morphine who converted to a 24-hour subcutaneous infusion of diamorphine via a syringe driver in the dying phase. Both the fentanyl group and the diamorphine group had good pain control in the last 48 hours of life. During the last 48 hours of life, the proportion of patients with controlled pain was statistically significant in favor of the fentanyl group in 2 of the 12 observations undertaken, in particular whether the fentanyl transdermal patch should be continued or discontinued. Patients in the fentanyl group received fewer "as required" opioid doses compared to patients in the diamorphine group, although the difference was statistically significant only for the last day of life. This study showed that pain control was not compromised in the dying phase with continued use of the fentanyl patch. Marie Curie Center, Speke Road, Woolton, Liverpool L25 8QA, United Kingdom.

- Elsner F, Radbruch L, Sabatowski R, Brunsch–Radbruch A, Loick G and Grond S (1999). [Switching opioids to transdermal fentanyl in a clinical setting]. *Schmerz* 13:273–8. Summary: INTRODUCTION: The use of transdermal fentanyl is gaining in importance in the management of cancer pain. We describe the reasons for switching opioid medication to transdermal fentanyl in a pain management unit. METHODS: Case records of patients treated with transdermal fentanyl in our pain clinic were evaluated retrospectively. Conversion ratios were calculated from the opioid dosage before and after conversion. Pain intensities were assessed on a numeric rating scale (NRS 0: no pain, 10: worst pain imaginable). RESULTS: From October 1995 to December 1997 101 patients received transdermal fentanyl. Thirty-six patients had been treated with transdermal fentanyl before admission to our pain clinic, and relevant information was missing for one patient, so 64 patients were evaluated.

Opioid therapy was switched to transdermal fentanyl during in-patient treatment for 53 patients and during out-patient treatment for 11 patients. Before conversion patients were treated with slow-release morphine (48%), immediate-release morphine (17%), buprenorphine (11%), tramadol (11%), levomethadone (5%), tilidine/naloxone (5%) and piritramid (3%). Reasons for opioid rotation were inadequate pain relief (33%), the patients' wish to reduce oral medication (20%), gastrointestinal side effects such as nausea (31%), vomiting (13%) and constipation (19%), dysphagia (27%) or others. Reduction of side effects was reported by 10 of 19 patients. In 12 of 21 patients, in whom the medication was switched because of inadequate pain relief, a reduction in pain intensity was reported. DISCUSSION: Conversion to transdermal therapy may readjust the balance between opioid analgesia and side effects. The opioid switch resulted in more pain relief or fewer side effects in half of the patients. A proposed equianalgesic conversion ratio between 70:1 and 100:1 from oral slow-release morphine to transdermal fentanyl can be confirmed by our data. Conversion rates from other opioids to transdermal fentanyl are suggested. Klinik und Poliklinik für Anesthesiologie und Operative Intensivmedizin, Universität Köln.

- Enting RH, Oldenmenger WH, van der Rijt CC, Wilms EB, Elfrink EJ, Elswijk I and Sillevs Smitt PA (2002). A prospective study evaluating the response of patients with unrelieved cancer pain to parenteral opioids. *Cancer* **94**:3049–56. Summary: BACKGROUND: The initiation of continuous parenteral (subcutaneous or intravenous) opioids or a change of opioid (opioid rotation) are treatment options for patients who fail on oral or transdermal opioids. There are insufficient data on the efficacy of these strategies, and comparative data are unavailable. METHODS: The authors prospectively evaluated the efficacy of the start of parenteral opioids in 100 patients with cancer pain who failed on conventional opioids. Pain intensity was rated at rest and during movement from 0 to 10 and was categorized as mild (0–4), moderate (5–6), or severe (7–10): Clinically important pain control was defined as a decrease ≥ 2 points in pain intensity and pain intensity < 7 . Pain control was evaluated on the second day and again when a clinical decision was made to continue or change parenteral opioid treatment after a median of 6 days. The presence of side effects (absent, mild, moderate, or severe) was evaluated. RESULTS: The mean pain intensity at rest decreased significantly from 6.3 to 4.4 at 48 hours and to 3.4 at the end of treatment. The mean pain intensity during movement decreased significantly from 8.4 to 5.7 at 48 hours and to 4.6 at the end of treatment. Clinically important pain control at rest was seen in 52% of patients at 48 hours, in 71% of patients at the end of treatment; and clinically important pain control during movement was seen in 43% of patients at 48 hours and in 61% of patients at the end of treatment. The

proportion of patients with mild pain increased significantly both at rest and during movement. Side effects were present in 78% of patients, and they resolved completely in 32% of patients. The median intravenous morphine equivalent dose increased from 80 mg per day to 135 mg per day at 48 hours and to 201 mg per day at the end of treatment. Results were not different for opioid rotation or for change of route only, nor did the start of antitumour treatment influence the results. In 34% of patients, it was decided to rotate to a second-line parenteral opioid or to start either spinal analgesia or a sedation procedure after a median of 6 days. During follow-up, 18% of patients who were dismissed with parenteral opioids (and 6% of all patients) needed a further change of treatment. CONCLUSIONS: Parenteral opioids improved the balance between analgesia and side effects in patients with cancer pain who failed on conventional opioids, with an important improvement seen in 71% of patients. On the basis of this study, it is concluded that parenteral opioids are a good alternative to spinal opioids. Furthermore, it is suggested that a change of route alone is as effective as opioid rotation. Department of Neuro-Oncology, Daniel den Hoed Cancer Center, University Hospital Rotterdam, Rotterdam, The Netherlands. enting@neuh.azr.nl

- Farrar JT, Cleary J, Rauck R, Busch M and Nordbrock E (1998). Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst* **90**:611–6. Summary: BACKGROUND: Patients with cancer frequently experience episodes of acute pain, i.e., breakthrough pain, superimposed on their chronic pain. Breakthrough pain is usually treated with short-acting oral opioids, most of which provide some relief after 15–20 minutes, with peak effects after 30–45 minutes. Oral transmucosal fentanyl citrate (OTFC), a unique formulation of the opioid fentanyl, has been shown to provide meaningful pain relief within 5 minutes in patients following surgery. We conducted a multicenter, randomized, double-blinded, placebo-controlled trial of OTFC for cancer-related breakthrough pain. METHODS: Patients who were 18 years of age or older, receiving the equivalent of at least 60 mg oral morphine or at least 50 microg transdermal fentanyl per day for chronic cancer-related pain, and experiencing at least one episode of breakthrough pain per day were studied. After titration to an effective OTFC dose, subjects were given 10 randomly ordered treatment units (seven OTFC units and three placebo units) in the form of identical lozenges. If acceptable pain relief was not achieved within 30 minutes, subjects were instructed to take their previous breakthrough pain medication (i.e., rescue medication). Pain intensity, pain relief, and use of rescue medication were evaluated at 15-minute intervals over a 60-minute period. RESULTS: Eighty-nine of 92 patients who received the randomized treatment were assessable (i.e.,

treated with at least one unit of OTFC and one unit of placebo). OTFC produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided $P < .0001$). Episodes treated with placebo required the use of rescue medication more often than episodes treated with OTFC (34% versus 15%; relative risk = 2.27; 95% confidence interval = 1.51–3.26; two-sided $P < .0001$).

CONCLUSIONS: OTFC appears effective in the treatment of cancer-related breakthrough pain. University of Pennsylvania School of Medicine, Philadelphia 19104, USA. farrar@cceb.med.upenn.edu

- Ferrell BR and McCaffery M (1997). Nurses' knowledge about equianalgesia and opioid dosing. *Cancer Nurs* **20**:201–12. Summary: Nurses are recognized as the cornerstone of palliative care. Yet, surveys of nurses' knowledge of cancer pain management reveal serious knowledge deficits that could adversely affect the care of patients with cancer pain. Previous research has explored basic pain management issues such as pain assessment and myths and misconceptions surrounding pain, and principles of analgesic use. Advances in recent years have increased the demand for continuing education that will extend scientific advances in pain to clinical practice. The purpose of this article is to share results from a study which evaluated nurses knowledge regarding three methods of analgesic delivery that have become common in clinical practice: intravenous morphine, extended release morphine, and transdermal fentanyl. Several resources are provided to assist clinicians in the appropriate use of these analgesic methods. City of Hope National Medical Center, Department of Nursing Research and Education, Duarte, CA 91010, USA.

- Fiset P, Cohane C, Browne S, Brand SC and Shafer SL (1995). Biopharmaceutics of a new transdermal fentanyl device. *Anesthesiology* **83**:459–69. Summary: BACKGROUND: Compared with conventional routes of delivering potent analgesics to postoperative patients, transdermal administration of fentanyl offers the advantages of simplicity and noninvasive delivery. The only available form of transdermal fentanyl, the Duragesic system, has been implicated in preventable patient deaths when used for postoperative analgesia and is contraindicated in the management of postoperative pain. We examined the biopharmaceutics of a new transdermal fentanyl device developed by Cygnus and intended for use as a postoperative analgesic to see whether the new formulation offers pharmacokinetic advantages that might permit safe use in postoperative patients. METHODS: We studied 15 consenting male adult surgical patients. Patients received 650 or 750 micrograms intravenous fentanyl as part of the induction of anesthesia. Plasma fentanyl concentrations were measured over the following 24-h period. On the first postoperative day, 24 h after the intravenous dose of fentanyl, a

transdermal fentanyl device was placed on the upper torso of the patient for 24 h and then removed. Plasma fentanyl concentrations were measured for 72 h after application of the transdermal fentanyl device. From the concentration versus time profile for the 24 h after intravenous fentanyl administration we determined each patient's clearance and unit disposition function by moment analysis and constrained numeric deconvolution, respectively. From the concentration versus time profile for the 72 h after application of the transdermal device we determined the amount of fentanyl absorbed and the rate of absorption, again by moment analysis and constrained numeric deconvolution. The residual fentanyl in the transdermal fentanyl device was measured, permitting calculation of the absolute bioavailability of transdermally administered fentanyl. RESULTS: Of the 14 subjects who received transdermal fentanyl, 3 had clinically significant fentanyl toxicity, mandating early removal of the device. The range during the plateau from 12 to 24 h in subjects still wearing the device was 0.34–6.75 ng/ml, a 20-fold range in concentration. In subjects wearing the device for 24 h, the terminal half-life of fentanyl after removal of the device was 16 h. The bioavailability of transdermally administered fentanyl was 63 +/- 35% coefficient of variation. The rate of fentanyl absorption from 12–24 h ranged from 10 to 230 micrograms/h in subjects still wearing the device. In two subjects, the rate within the first 6 h briefly exceeded 300 micrograms/h. Both of these subjects demonstrated fentanyl toxicity, requiring early removal of the device. CONCLUSIONS: The Cygnus transdermal fentanyl device shows great variability in the rate of fentanyl absorption, resulting in highly variable plasma fentanyl concentrations. Some persons may rapidly absorb fentanyl from the device in the first few hours after application, leading to fentanyl toxicity. The variability in effect of the Cygnus transdermal fentanyl device is appreciably greater than that reported for the currently available Duragesic transdermal fentanyl device, which is contraindicated for postoperative analgesia. Department of Anaesthesia, McGill University, Montreal, Quebec, Canada.

- Frolich MA, Giannotti A, Modell JH and Frolich M (2001). Opioid overdose in a patient using a fentanyl patch during treatment with a warming blanket. *Anesth Analg* 93:647–8. Summary: IMPLICATIONS: This case describes the narcotic overdose associated with the use of a fentanyl transdermal patch in a patient being rewarmed with an external warming blanket during surgery. The clinical manifestation and the presumed pharmacokinetic mechanism responsible for the fentanyl overdose are discussed. Department of Anesthesiology, University of Florida Colleges of Medicine and Veterinary Medicine, Gainesville, Florida, USA. froelich@anest.ufl.edu

- Gardner–Nix J (2001). Caregiver toxicity from transdermal fentanyl. *J Pain Symptom Manage* **21**:447–8. Summary:
- Goldstein JA (2001). Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol* **52**:349–55. Summary: The human CYP2Cs are an important subfamily of P450 enzymes that metabolize approximately 20% of clinically used drugs. There are four members of the subfamily, CYP2C8, CYP2C9, CYP2C19, and CYP2C18. Of these CYP2C8, CYP2C9, and CYP2C19 are of clinical importance. The CYP2Cs also metabolize some endogenous compounds such as arachidonic acid. Each member of this subfamily has been found to be genetically polymorphic. The most well-known of these polymorphisms is in CYP2C19. Poor metabolizers (PMs) of CYP2C19 represent approximately 3–5% of Caucasians, a similar percentage of African-Americans and 12–100% of Asian groups. The polymorphism affects metabolism of the anticonvulsant agent mephenytoin, proton pump inhibitors such as omeprazole, the anxiolytic agent diazepam, certain antidepressants, and the antimalarial drug proguanil. Toxic effects can occur in PMs exposed to diazepam, and the efficacy of some proton pump inhibitors may be greater in PMs than EMs at low doses of these drugs. A number of mutant alleles exist that can be detected by genetic testing. CYP2C9 metabolizes a wide variety of drugs including the anticoagulant warfarin, antidiabetic agents such as tolbutamide, anticonvulsants such as phenytoin, and nonsteroidal anti-inflammatory drugs. The incidence of functional polymorphisms is much lower, estimated to be 1/250 in Caucasians and lower in Asians. However, the clinical consequences of these rarer polymorphisms can be severe. Severe and life-threatening bleeding episodes have been reported in CYP2C9 PMs exposed to warfarin. Phenytoin has been reported to cause severe toxicity in PMs. New polymorphisms have been discovered in CYP2C8, which metabolizes taxol (paclitaxel). Genetic testing is available for all of the known CYP2C variant alleles. Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA. Goldstel@niehs.nih.gov
- Grilo RM, Bertin P, Scotto di Fazano C, Coyral D, Bonnet C, Vergne P and Treves R (2002). Opioid rotation in the treatment of joint pain. A review of 67 cases. *Joint Bone Spine* **69**:491–4. Summary: OBJECTIVE: To determine that opioid rotation can be useful for establishing a more advantageous analgesia/toxicity relationship in rheumatologic pain. METHODS: Among patients treated with opioids for rheumatologic non-malignant pain, 67 patients with opioid rotation were enrolled retrospectively. In all cases, the other analgesics had failed. The opioids used were: oral morphine, oral hydromorphone, oral buprenorphine and transdermal fentanyl. The reasons for rotation were noted and the

improvement of pain was assessed by comparing baseline and post-treatment visual analog scales (VAS in mm). RESULTS: The 67 patients suffered from low back pain with sciatica in 27 cases, inflammatory arthritis in 14 cases, brachial neuralgia in six cases, osteoarthritis in eight cases and miscellaneous in 12 cases. The opioid rotations were the substitution of morphine by transdermal fentanyl, by oral hydromorphone in most of the cases. The principal reason for opioid rotation was failure of the first treatment. The mean of VAS improvement was 30 mm ($P < 0.001$). CONCLUSION: In rheumatologic non-malignant pain, the opioid rotation might allow the physician to bypass side effects or failure to alleviate pain in most cases. Rheumatology and Therapeutics Department, CHU Dupuytren, 2 avenue Martin Luther King, 87042 Limoges, France.

- Grond S, Radbruch L and Lehmann KA (2000). Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. *Clin Pharmacokinet* 38:59–89. Summary: Transdermal delivery allows continuous systemic application of opioids through the intact skin. This review analyses the pharmacokinetic properties of transdermal opioid administration in the context of clinical experience, with a focus on fentanyl. A transdermal therapeutic system (TTS) for fentanyl has been developed. The amount of fentanyl released is proportional to the surface area of the TTS, which is available in different sizes. After the first application of a TTS, a fentanyl depot concentrates in the upper skin layers and it takes several hours until clinical effects are observed. The time from application to minimal effective and maximum serum concentrations is 1.2 to 40 hours and 12 to 48 hours, respectively. Steady state is reached on the third day, and can be maintained as long as patches are renewed. Within each 72-hour period, serum concentrations decrease gradually over the second and third days. When a TTS is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot. The terminal half-life for TTS fentanyl is approximately 13 to 25 hours. The interindividual variability of serum concentrations, partly caused by different clearance rates, is markedly larger than the intraindividual variability. The effectiveness of TTS fentanyl was first demonstrated in acute postoperative pain. However, the slow pharmacokinetics and large variability of TTS fentanyl, together with the relatively short duration of postoperative pain, precluded adequate dose finding and led to inadequate pain relief or, especially, a high incidence of respiratory depression; such use is now contraindicated. Conversely, in cancer pain, TTS fentanyl offers an interesting alternative to oral morphine, and its effectiveness and tolerability in this indication has been demonstrated by a number of trials. Its usefulness in chronic pain of nonmalignant origin remains to be confirmed in controlled trials. In general, TTS fentanyl produces the same

adverse effects as other opioids, mainly sedation, nausea, vomiting and constipation. In comparison with oral morphine, TTS fentanyl causes fewer gastrointestinal adverse events. The risk of hypoventilation is comparatively low in cancer patients. Sufentanil and buprenorphine may also be suitable for transdermal delivery, but clinical results are not yet available. Transdermal morphine is only useful if applied to de-epithelialised skin. However, iontophoresis may allow transdermal administration of opioids, including morphine, with a rapid achievement of steady state concentrations and the ability to adjust delivery rates. This would be beneficial for acute and/or breakthrough pain, and initial clinical trials are in progress. Department of Anaesthesiology, University of Cologne, Germany. stefan.grond@uni-koeln.de

- Gupta SK, Bernstein KJ, Noorduyn H, Van Peer A, Sathyan G and Haak R (1998a). Fentanyl delivery from an electrotransport system: delivery is a function of total current, not duration of current. *J Clin Pharmacol* 38:951–8. Summary: This open-label, parallel study of 28 men was conducted to evaluate the pharmacokinetics and safety of fentanyl delivered by the E-TRANS (fentanyl) electrotransport transdermal system (ALZA Corporation, Palo Alto, CA). The E-TRANS (fentanyl) system provided electrically assisted, transdermal, continuous delivery of fentanyl. Treatments consisted of no current (group A); a constant current of 100 microA for 26 hours plus 4 additional doses at varying currents for varying times during hour 25 (groups B, C, D); a constant current of 100 microA for 26 hours plus 4 additional doses at 1,200 microA over 2.5 minutes during hour 1 (group E); or 500 microA for 0.5 hours and 100 microA for 3.5 hours (group F). No fentanyl was detected in serum when no current had been applied. Mean serum fentanyl concentrations were similar regardless of current duration during hour 25 (treatments B, C, D). Increases in mean serum fentanyl concentrations were significantly lower during additional dosing for treatment E compared with treatments B, C, and D. Serum fentanyl concentrations sufficient for analgesia (1–3 ng/mL) were attained in treatments using the E-TRANS (fentanyl) system with basal current of 100 microA for 26 hours. There were no safety issues after treatment with E-TRANS (fentanyl) system with concurrent opioid antagonist (naltrexone) administration. The only adverse event requiring treatment was a headache (n = 1). The majority of subjects had no or barely perceptible erythema at the application site 24 hours after system removal. Application of E-TRANS (fentanyl) resulted in therapeutically significant serum fentanyl concentrations over a range of applied currents. Overall serum fentanyl concentrations were higher when the skin had been primed by constant-current fentanyl delivery. Department of Clinical Pharmacology, ALZA Corporation, Mountain View, California 94039–7210, USA.

- Gupta SK, Sathyan G, Phipps B, Klausner M and Southam M (1999). Reproducible fentanyl doses delivered intermittently at different time intervals from an electrotransport system. *J Pharm Sci* **88**:835–41. Summary: The electrotransport transdermal fentanyl system (ET [fentanyl]), uses a small electrical current to enhance delivery of fentanyl to systemic circulation. Intermittent doses can be administered by periodic application of the current. The purpose of this study was to compare the effects of the frequency of intermittent drug delivery by ET (fentanyl) and compare the drug delivery to systemic circulation by ET (fentanyl) with intravenous administration. The topical safety was also determined for the ET (fentanyl) system. Nine adult male volunteers completed this three-treatment, randomized, 24-h, crossover study. ET (fentanyl) treatments with 200 microA direct current applied for 30 min at frequent (hourly) or infrequent (4-hourly) intervals over a 24-h period were compared. Also, the drug delivery to systemic circulation from ET (fentanyl) was compared with intravenous fentanyl 75 microg infused over 30 min every 4 h over a 24-hour period. The mean serum fentanyl concentration achieved with the hourly ET (fentanyl) regimen was higher than that for the 4-hourly ET (fentanyl) regimen as expected from the higher frequency of drug doses. The amount of fentanyl delivered estimated per dose from the ET (fentanyl) system using the iv fentanyl treatment as the reference was similar for the two ET regimens throughout the dosing period. This indicates consistent drug delivery regardless of the frequency of ET dosing. The majority of subjects reported either no, or barely perceptible, erythema 24 h after removal of the system. ALZA Corporation, 950 Page Mill Road, Palo Alto, California 94303, and Janssen Pharmaceutica, 11225 Trenton Harbourton Rd., Titusville, New Jersey 08560, USA.
- Gupta SK, Southam M, Sathyan G and Klausner M (1998b). Effect of current density on pharmacokinetics following continuous or intermittent input from a fentanyl electrotransport system. *J Pharm Sci* **87**:976–81. Summary: The pharmacokinetics of fentanyl were determined in two open-label crossover studies following 24-h periods of delivery by an electrotransport transdermal system (E-TRANS [fentanyl] system) in young healthy male volunteers. A direct current was applied continuously in study 1 (at 50, 100, and 200 microA; surface area = 5 cm²; n = 8), but in study 2 it was limited to the first 20 min of each hour (at 150, 200, and 250 microA; surface area = 2 cm²; n = 12). The opioid effects of fentanyl were blocked with naltrexone administered every 12 h. With increasing electrical current, the increase in serum fentanyl concentration, amount absorbed, and AUC values were proportional in study 2 but not in study 1. It is hypothesized that the lack of proportionality in study 1 is due to lower current density (microA/cm²) in this study. It appears that for fentanyl, the current density should be

about 75 microA/cm² or greater for a linear relation between current and amount absorbed as seen in study 2. Compared with intravenously infused fentanyl, the serum concentrations resulting from E-TRANS (fentanyl) system application revealed a slightly dampened rate of increase (stratum–corneum barrier effect) and decrease in serum concentrations, and a similar intersubject variability in fentanyl AUC values. Fentanyl pharmacokinetics with either E-TRANS (fentanyl) or intravenous infusion were time–invariant over a 24–h application period, with similar mean half–life values (about 15–18 h). E-TRANS (fentanyl) administration (either continuous or intermittent input) was safe and well tolerated. Adverse effects were mild to moderate; they consisted mainly of local erythema and pruritus (which resolved in most patients within 24 h after system removal) and occasional opioid effects. ALZA Corporation, 1550 Plymouth Street, P.O. Box 7210, Mountain View, California 94039–7210, USA. suneel.gupta@alza.com

- Han PK, Arnold R, Bond G, Janson D and Abu–Elmagd K (2002). Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. *J Pain Symptom Manage* 23:66–72. Summary: Myoclonus is a common and well–described adverse effect of opioids. Most cases reported in the literature have been associated with opioid administration, rather than with opioid withdrawal. We describe a case of myoclonus secondary to withdrawal from transdermal fentanyl. We review the literature regarding myoclonus related to opioid therapy (opioid–induced myoclonus) and withdrawal (opioid withdrawal myoclonus), and discuss possible mechanisms and therapies for these phenomena. Section of Palliative Care and Medical Ethics Division of General Internal Medicine, University of Pittsburgh Medical Center, 5320 Centre Avenue, Pittsburgh, PA 15232, USA.
- Henderson GL (1991). Fentanyl–related deaths: demographics, circumstances, and toxicology of 112 cases. *J Forensic Sci* 36:422–33. Summary: Since 1979, the potent narcotic analgesic fentanyl and its analogs have been synthesized in clandestine laboratories and sold as heroin substitutes. At least 112 overdose deaths have been associated with their use. In this study, toxicology data, autopsy findings, and coroners' investigative reports were reviewed in order to construct a profile of the typical fentanyl overdose victim and to identify any factors that might heighten the risk of death from fentanyl use. The "typical" fentanyl overdose victim was 32.5 +/- 6.7 years of age (range, 19 to 57 years), male (78%, compared with 22% female), and Caucasian (50%, compared with 29% Hispanic, 20% Black, and 0.9% Asian). With the exception of his or her age, the typical fentanyl overdose victim is quite similar to the typical heroin user. Nearly all the deaths (94%) occurred in California, yet within the state they were widely distributed throughout 17

counties and 44 cities. Pulmonary edema and congestion and needle puncture sites were consistent postmortem findings. No preexisting medical conditions were identified as possible risk factors. Although most of the fentanyl victims had a prior history of intravenous drug use, morphine or codeine were not commonly found, which suggests that the victims had little or no opiate tolerance. Ethanol was present in 38% of the cases and is thought to be a significant risk factor. Mean fentanyl concentrations in the body fluids were quite low: 3.0 +/- 3.1 ng/mL (0.3 +/- 0.31 micrograms/dL) in blood and 3.9 +/- 4.3 ng/mL (0.39 +/- 0.43 micrograms/dL) in urine, measured by radioimmunoassay. Although the potency of the analogs and the purity of street samples varies considerably, it is probably the general availability of the drug rather than the potency of a particular analog that determines the incidence of overdose deaths. Department of Pharmacology, School of Medicine, University of California–Davis.

- Hunt A, Goldman A, Devine T and Phillips M (2001). Transdermal fentanyl for pain relief in a paediatric palliative care population. *Palliat Med* 15:405–12. Summary: This multicentre, observational study examined the efficacy of the therapeutic transdermal fentanyl system (TTS–fentanyl) in children requiring opioids for pain in life–threatening disease. Forty–one children receiving oral morphine (median dose 60 mg/day) transferred to transdermal fentanyl (median dose 25 micrograms/h according with the manufacturer's dose conversion guidelines). Twenty–six children completed the 15–day treatment phase, seven died due to disease progression and eight were withdrawn because of adverse events, inadequate analgesia or a change to parenteral opioids. After 15 days, the median fentanyl dose was 75 micrograms/h (range 25–250). No serious adverse events were attributed to fentanyl. There was a trend toward improved side–effects and convenience with fentanyl. Twenty–three of 26 parents (three missing) and 25 of 26 investigators considered transdermal fentanyl to be better than previous treatment. For all records available (at 15 days or on withdrawal if earlier), 75% (27/36) reported that fentanyl treatment was 'good' or 'very good'. The findings suggest that transdermal fentanyl is both effective and acceptable for children and their families. Institute of Child Health, London, UK. anne.hunt@rcn.org.uk

- Iconomou G, Viha A, Vagenakis AG and Kalofonos HP (2000). Transdermal fentanyl in cancer patients with moderate–to–severe pain: a prospective examination. *Anticancer Res* 20:4821–4. Summary: BACKGROUND: The aim of the study was to evaluate prospectively the analgesic efficacy, toxicity and acceptability of the transdermal fentanyl therapeutic system (TTS–F) in Greek cancer patients with moderate–to–severe pain. METHODS: Forty–eight patients participated in the study: 34

were men and 14 women, mean age was 63, and all but 2 had advanced stage (IV) cancer. Patients received TTS-F for a period of 8 weeks. Doses ranged from 25 to 225 micrograms/h. Thirty-three patients completed the study. RESULTS: Data indicated statistically significant lower pain scores on both NRS and EORTC QLQ-C30 at all follow-ups compared to baseline. In addition, the vast majority of the patients found the transdermal system easy to use and reported as being satisfied or highly satisfied with it. The only observed side-effect was vomiting.

CONCLUSION: In summary, transdermal fentanyl appeared an acceptable, safe and effective method of managing chronic pain induced by malignancies. University of Patras Medical School, Department of Medicine-Division of Oncology, University Hospital, Rion 265 00, Greece.

- Jorum E, Warncke T and Stubhaug A (2003). Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine--a double-blind, cross-over comparison with alfentanil and placebo. *Pain* **101**:229-35. Summary: Cold allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. While there have been several clinical studies showing the involvement of central sensitization mechanisms and N-methyl-D-aspartate (NMDA) receptor activation in mechanical allodynia/hyperalgesia and ongoing pain, the mechanisms of thermal allodynia and hyperalgesia have received less attention. The aim of the present study was to examine the effect of the NMDA-receptor antagonist ketamine on thermal allodynia/hyperalgesia, ongoing pain and mechanical allodynia/hyperalgesia in patients with neuropathic pain (11 patients with post-traumatic neuralgia and one patient with post-herpetic neuralgia). All the patients were known to suffer from severe cold allodynia (cold pain detection threshold (CPDT): 23.8 degrees C, median value). The mu-opioid agonist alfentanil was used as an active control. The study design was double-blind and placebo-controlled and the drugs were administered i.v. (bolus dose and infusion). CPDT in the asymptomatic contralateral area was found to be significantly decreased (cold allodynia) compared to CPDT in site- and age-matched normal controls. Heat pain detection thresholds were found to be normal and no consistent heat hyperalgesia occurred. Alfentanil significantly reduced cold allodynia (by increasing CPDT) in symptomatic area (P=0.0076). Ketamine did not significantly increase the threshold. Significant and marked reductions of hyperalgesia to cold (visual analogue score at threshold value) were seen following both alfentanil (4.5 before, 1.4 after, median value) and ketamine (6.8 before, 0.4 after, median value). Alfentanil and ketamine also significantly reduced ongoing pain and mechanical hyperalgesia. It is concluded that NMDA-receptor mediated central sensitization is involved in cold hyperalgesia, but since CPDT remained unaltered, it is likely that other mechanisms are present.

Department of Neurology, The National Hospital, University of Oslo, 0027 Oslo, Norway.

- Klockgether–Radke A and Hildebrandt J (1997). [Opioid intoxication. Inappropriate administration of transdermal fentanyl]. *Anaesthesist* **46**:428–9. Summary: A 22–year–old male suffering from neuropathic pain in his right leg had sufficient analgesia with oral tilidin 300 mg per day. Nevertheless, the general practitioner decided to change the therapy to transdermal fentanyl. Having cut a fentanyl patch (50 micrograms/h) into pieces, he applied one–fourth of the patch; 60 min later the patient developed signs of opioid intoxication, including heavy sedation, nausea and respiratory depression. After the patch was removed another 60 min later, the patient made a complete recovery. The risks following inappropriate application of transdermal fentanyl are discussed. Schwerpunkt Algesiologie, Zentrum Anaesthesiologie, Rettungs– und Intensivmedizin, Georg–August–Universitat Gottingen.
- Klockgether–Radke AP, Gaus P and Neumann P (2002). [Opioid intoxication following transdermal administration of fentanyl]. *Anaesthesist* **51**:269–71. Summary: The case of a 77–year–old woman is described, who was found unconscious, with decreased respiration and miotic pupils, having previously experienced dizziness, nausea and drowsiness before. In the emergency room a fentanyl patch was detected, which had obviously been mistakenly applied by the patient the day before. Opioid intoxication was assumed and successfully treated with naloxon. The patient was supervised in an ICU for 24 h and sent home the next day without serious sequelae. The consequences following inappropriate use of transdermal fentanyl are discussed. Zentrum Anaesthesiologie, Rettungs– und Intensivmedizin, Georg–August–Universitat Gottingen, Robert–Koch–Strasse 40, 37075 Gottingen. Klockgether–Radke@gmx.de
- Kongsgaard UE and Poulain P (1998). Transdermal fentanyl for pain control in adults with chronic cancer pain. *Eur J Pain* **2**:53–62. Summary: The transdermal therapeutic system (TTS) for fentanyl is a drug–delivery system for use in patients with chronic pain who require an opioid analgesic. A multicentre, randomized, double–blind, placebo–controlled study was performed to evaluate the efficacy and safety of TTS–fentanyl as an analgesic for chronic cancer pain. One hundred and thirty–eight patients entered a 15–day dose–titration period, followed by a 9–day double–blind period (95 patients) with TTS–fentanyl or placebo. Fifty–five patients entered a follow–up period of indefinite duration. For the majority of patients, TTS–fentanyl 50–75 microg/h provided effective analgesia. Due to an unexpectedly high placebo response, it was not possible to show fentanyl to be statistically superior to placebo at the 5%

significance level. Nine patients treated with fentanyl and 13 treated with placebo were withdrawn from the study during the double-blind therapy because of insufficient efficacy (not significant), while 66% of fentanyl-treated patients experienced effective pain control compared with 48% of placebo-treated patients ($p=0.071$). During the course of the double-blind therapy, the mean dose of rescue morphine increased slightly more in the placebo group than in the fentanyl group. At the end of the double-blind phase, the investigators rated trial medication as being 'good' or 'excellent' in 30 patients in the fentanyl group and 23 in the placebo group. TTS-fentanyl appeared to be well tolerated, with a low incidence of constipation, somnolence and nausea. Due to an unexpectedly high placebo response it was not possible to demonstrate fentanyl to be statistically superior to placebo. This may reflect the practical difficulties of performing clinical trials in cancer patients with great inter-individual variability. Copyright 1998 European Federation of Chapters of the International Association for the Study of Pain. The Norwegian Radium Hospital, Montebello, Oslo, Norway

- Kornick CA, Santiago-Palma J, Khojainova N, Primavera LH, Payne R and Manfredi PL (2001). A safe and effective method for converting cancer patients from intravenous to transdermal fentanyl. *Cancer* **92**:3056-61. Summary: BACKGROUND: Therapeutic fentanyl blood levels are reached approximately 12-16 hours after the initial application of transdermal fentanyl patches. For this reason, fentanyl patches should not be used to treat acute exacerbations of cancer pain. Acute cancer-related pain can be treated with fentanyl administered by continuous intravenous infusion (CII) in combination with patient-controlled analgesia (PCA). Patients then can be switched from intravenous (IV) to transdermal fentanyl once stable pain relief has been achieved. The objective of the current case series was to evaluate and describe the safety and effectiveness of a method for converting hospitalized patients with cancer-related pain from IV to transdermal fentanyl. METHODS: The authors prospectively evaluated 15 consecutive cancer patients during the conversion from IV to transdermal fentanyl. In all patients, a transdermal patch delivering fentanyl at a rate equivalent to that of the final continuous IV infusion was applied. The CII rate was decreased by 50% 6 hours after application of the fentanyl patch and then discontinued after another 6 hours. Demand boluses of IV fentanyl equivalent in dosage to 50-100% of the final CII rate remained available via PCA during the 24 hours after patch application. Pain intensity (on a scale of 0-10), sedation (on a scale of 0-3), and hourly PCA administration (microg/hr) were assessed and recorded immediately prior to application of the fentanyl patch and 6, 12, 18, and 24 hours thereafter. RESULTS: Pain intensity, sedation, and hourly PCA administration appeared to remain stable throughout the transition from IV to transdermal fentanyl. CONCLUSIONS: The results of the current

study demonstrate that the conversion from IV to transdermal fentanyl can be accomplished safely and effectively using a 1:1 (IV:transdermal) conversion ratio and a two-step taper of the CII over 12 hours. Pain and Palliative Care Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.

- Korte W, de Stoutz N and Morant R (1996). 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* **11**:139-46. Summary: Initial dose finding in patients with cancer pain who are started on TTS fentanyl (Duragesic, TTS-F) is often unsatisfactory with currently recommended doses and intervals. Acknowledging that studies reveal a "psuedo steady state" 15 to 20 hr after application of TTS-F, we prospectively investigated an increased initial dose and day-to-day titration of TTS-F in 39 (evaluatable) patients with uncontrolled cancer pain. Significant pain reduction ($P = 0.001$) was seen after 24 hr, and satisfactory analgesia was achieved within 48 h and maintained for the rest of the study. Significant increases in TTS-F were necessary during weeks 1 through 4 to maintain pain control. Forty-nine percent of the patients needed one or more early dose increases. Only one patient had side effects partially due to the specific properties of the TTS. Other side effects seemed to be less common compared with usual morphine treatment. TTS-F can be titrated effectively and safely on a day-to-day basis with an increased initial dose and adequate patient monitoring, thus avoiding more complicated approaches. TTS-F seemed to induce less constipation than might be expected. Division of Oncology, University of Colorado Health Science Center, Denver 80262, USA.

- Kramer C and Tawney M (1998). A fatal overdose of transdermally administered fentanyl. *J Am Osteopath Assoc* **98**:385-6. Summary: We present a case of fentanyl overdose via mucous membrane absorption. A 31-year-old man presented to the emergency department in respiratory arrest. At intubation, a Duragesic transdermal patch (75 micrograms/h) was recovered from the buccal cavity. A second fentanyl transdermal patch (75 micrograms/h) was noted on the right lateral aspect of the thigh. Postmortem blood evaluation returned a venous fentanyl level of 17.2 micrograms/L. The therapeutic range for analgesic use is 1 microgram/L to 3 micrograms/L. Drug screens were positive for benzodiazepines and cocaine. Mass spectrophotometry/gas chromatography was used to determine fentanyl levels and to confirm drug screen results. Case history, findings at intubation, and high fentanyl blood concentration suggest the cause of respiratory arrest and death was fentanyl overdose. Mount Clemens General Hospital, Department of Emergency Medicine, MI 48043, USA. CKramer%PCS@MCGH.org

- Laval G, Sang B, Mallaret M and Villard ML (2002). [New Level III opioids of the World Health Organization]. *Rev Med Interne* 23:55–70. Summary: PURPOSE: The new opioids and the new galenic forms, now available in France, require an update in practitioners' knowledge. The purpose of the present study is to help those prescribing select the appropriate opioid and its galenic form for pain relief. CURRENT KNOWLEDGE AND KEY POINTS: Presentation of pharmacological properties of opioids (mechanisms, pharmacokinetics and pharmacovigilance). Presentation of indications, modes of prescription and use of main opioids for pain (especially cancer pain). Examples for calculating required drug dosage depending on the clinical situation and the route of administration. Symptomatic treatments of the main undesirable side effects of the opioids, and actions to be taken in the event of accidental overdose. FUTURE PROSPECTS AND PROJECTS: Oral morphine is the treatment first recommended for nociceptive pain insufficiently relieved by WHO level I and II analgesics. The new immediate–release galenic forms allow morphine titration and the treatment of breakthrough pain. Transmucosal fentanyl, soon available in France, is recommended for breakthrough pain in patients already under opioid treatment: it gives more rapid relief starting after only 5 minutes and it only acts for a short time. Transdermal fentanyl is indicated for stable cancer pain. It is particularly suitable when oral and injectable morphine routes are not available, or for patients with severe constipation. Hydromorphone is the first opioid recommended in France for severe cancer pain when morphine resistance exists or uncontrolled side effects are present (opioid rotation). The new opioids and the new galenic forms widen the range of therapeutic possibilities. Their use is well codified for cancer pain and must still undergo clinical trials for chronic non–cancer pain. When correctly indicated, opioid selection provides a considerable advance in pain management. Unite de recherche et de soutien en soins palliatifs, CHU, BP 217, 38043 Grenoble, France. GLaval@chu–grenoble.fr
- Lawrie I, Lloyd–Williams M and Waterhouse E (2003). Breakthrough strong opioid analgesia prescription in patients using transdermal fentanyl admitted to a hospice. *Am J Hosp Palliat Care* 20:229–30. Summary: Duragesic (fentanyl) patches have revolutionized pain relief, but patients still require breakthrough medication. A retrospective analysis of in–patient admission notes at a 25–bed hospice over a six–month period was carried out. Details of analgesia being used on admission for both background and breakthrough pain were obtained, and the appropriateness of the breakthrough dose for those patients using transdermal fentanyl was determined. During the study period 278 patients were admitted to the hospice and 56 (20 percent) were using transdermal fentanyl. Of these, 35 (62 percent) were prescribed strong

opioid analgesia--the dose of breakthrough medication prescribed was appropriate in 11 patients (31 percent). Rescue dosing was less than recommended, in relation to prescribed transdermal fentanyl strength in 21 patients (60 percent) and greater than recommended in one patient (3 percent). In this study, short-acting strong opioid analgesia was not always prescribed for patients using transdermal fentanyl, and when they were prescribed, this was in the appropriate dose range in less than a third of patients. Leicestershire Hospice, Leicester, England.

- Leung A, Wallace MS, Ridgeway B and Yaksh T (2001). Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain* **91**:177-87. Summary: Both mu opioid agonists and N-methyl-D-aspartate (NMDA) receptor antagonists are implicated in the regulation of neuropathic pain in post-nerve injury preclinical pain models. This study characterizes the effects of intravenously infused alfentanil (a mu-receptor agonist) and ketamine (an NMDA-receptor antagonist) on human neuropathic pain states, characterized by allodynia and hyperalgesia. Using diphenhydramine as the placebo, alfentanil and ketamine infusions were given in a randomized double-blind fashion 1 week apart via a computer-controlled infusion (CCI) pump that was programmed to target plasma levels of alfentanil at 25, 50 and 75 ng/ml and ketamine at 50, 100 and 150 ng/ml. At the beginning of each infusion and each targeted plasma level, baseline vital signs, neurosensory testing that included thermal thresholds, thermal pain and von Frey filament thresholds, and spontaneous and evoked pain scores were obtained. Moreover, the areas of allodynia or hyperalgesia to stroking and a 5.18 von Frey filament were mapped at the beginning and the end of each infusion. A total of seven males and five females with post-nerve injury allodynia and hyperalgesia were enrolled in the study. Elevations of cold, warm, hot pain and von Frey tactile thresholds were noted. Dose-dependent increases in cold and cold pain thresholds, and reductions in stroking pain scores were noted in both the alfentanil and the ketamine infusions. In addition, alfentanil showed a statistically significant dose-dependent reduction in both spontaneous and von Frey pain scores. Both the alfentanil and ketamine infusions showed a reduction in the stroking hyperalgesic area and ketamine showed a significant reduction in the von Frey hyperalgesia area. No significant CNS side effects and changes in vital signs were noted. A partial deafferentation state was found in the post-nerve injury patients who presented with allodynia and hyperalgesia. The effects of alfentanil on cold and cold pain thresholds and spontaneous pain scores correlates with previous studies suggesting an opiate central analgesic effect. In addition, the reduction of the hyperalgesic area and evoked pain scores with the alfentanil infusion suggests that opioids may have some peripheral effects in the post-nerve injury patients. Therefore, clinical

utilization of opioids with careful titration may be beneficial in post-nerve injury patients with partial deafferentation. With the absence of significant CNS side effects, the ketamine infusion not only demonstrated the well-documented spinal cord mechanism of the NMDA receptor, but the result of the current study also suggests that a peripheral mechanism of NMDA receptor may exist. The relationship between central sensitization and regulation of peripheral NMDA-receptor expression requires further investigation. Department of Anesthesiology, University of California, San Diego, 9500 Gilman Drive #0924, La Jolla, CA 92093-0924, USA.

- Lotsch J, Skarke C, Tegeder I and Geisslinger G (2002). Drug interactions with patient-controlled analgesia. *Clin Pharmacokinet* 41:31-57. Summary: Patient-controlled analgesia (PCA) has become standard procedure in the clinical treatment of pain. Its widespread use in patients with all kinds of diseases opens a variety of possible interactions between analgesics used for PCA and other drugs that might be administered concomitantly to the patient. Many of these drug interactions are of little clinical importance. However, some drug interactions have been reported to result in serious clinical problems. Drug interactions can either predominantly affect the pharmacokinetics or pharmacodynamics of the drug. Most important pharmacokinetic drug interactions occur at the level of drug metabolism or protein binding. Acceleration of methadone metabolism caused by cytochrome P450 (CYP) 3A4 induction by antiretroviral drugs or rifampicin (rifampin) has caused methadone withdrawal symptoms. Lack of morphine formation from codeine as a result of CYP2D6 inhibition by quinidine results in an almost complete loss of the analgesic effects of codeine. Alterations of methadone protein binding caused by an inhibition of alpha1-acid glycoprotein synthesis by alkylating substances are another possibility for predominantly pharmacokinetically based drug interactions during PCA. Furthermore, inhibition of P-glycoprotein by anticancer drugs could result in altered transmembrane transport of morphine, methadone or fentanyl, although this has not been shown to be of clinical relevance. Synergistic effects of systemically administered opioids with spinally or topically delivered opioids or anaesthetics have been reported frequently. The same is true for the opioid-sparing effects of coadministered non-opioid analgesics. Antidepressants, anticonvulsants or alpha2-adrenoreceptor agonists have also been shown to exert additive analgesic effects when administered together with an opioid. Inconsistent findings, however, are reported regarding the treatment of patients with opioid-induced nausea and sedation, since coadministration of antiemetics either increased or decreased the respective adverse effects or revealed additional unwanted drug effects. Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt, Germany. j.loetsch@em.uni-frankfurt.de

- MacKay S (1993). Pain corner. Duragesic. AARN News Lett **49**:16. Summary:
- Mannerkoski MK, Heiskala HJ, Santavuori PR and Pouttu JA (2001). Transdermal fentanyl therapy for pains in children with infantile neuronal ceroid lipofuscinosis. Eur J Paediatr Neurol **5 Suppl A**:175–7. Summary: We used infantile neuronal ceroid lipofuscinosis (INCL), in which deterioration of the central nervous system is extremely rapid, to study constant release of an opioid for pains of central origin in a metabolic disease. The effect of a transdermal fentanyl patch was studied in five children with INCL. In two of them, measurements of 17 fentanyl serum concentrations and also visual analogue pain scale were obtained during a 15-day study period. Low doses of transdermal fentanyl usually provided good pain relief for the first two days, but not for the third day, of the three-day patch change interval. Pain relief of this type seems mandatory for pains mostly of central origin. Department of Child Neurology, Hospital for Children and Adolescents, University of Helsinki, Finland.
- Mantovani G, Curreli L, Maccio A, Massa E, Massa D, Mulas C, Succu G and Contu P (1999). 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 **19**:3495–502. Summary: A single-institution, prospective, open crossover study was performed to compare the effectiveness and tolerability of transdermal fentanyl (TTS-F) vs intravenous (i.v.) ondansetron (OND), both combined with i.v. DEX, in the prevention of acute nausea and vomiting (N&V), and TTS-F vs metoclopramide (M), both combined with intramuscular (i.m.) DEX, in the prevention of delayed N&V in patients with advanced stage head and neck squamous cell carcinoma receiving high-dose ($> \text{ or } = 100 \text{ mg/m}^2$) cisplatin. This is the first report on the clinical use of TTS-F in this setting. PATIENTS AND METHODS: All patients were adequately informed of the study characteristics and gave their written informed consent before study entry. The antiemetic treatment for acute N&V consisted of A) OND 8 mg plus DEX 20 mg (i.v.) or B) TTS-F 75 micrograms/h plus DEX 20 mg i.v. For prevention of delayed N&V, patients receiving TTS-F for acute N&V were given TTS-F at the same dosage (75 micrograms/h) on days 2–5, whereas patients receiving OND for acute N&V were treated with M 20 mg orally every 6 h on days 2–5, starting 24 h after CDDP. All patients received DEX 8 mg i.m. every 12 h on days 2 and 3, 4 mg i.m. every 12 h on days 4 and 5, starting 24 h after CDDP. From November 1997 to April 1998, 15 consecutive patients entered the study and were assigned to

one of the two alternative treatments for acute N&V. All of them were evaluable. Twelve patients were evaluable for delayed N&V. Seven patients were assigned to Group 1 starting with treatment A (OND + DEX) and 8 patients were assigned to Group 2 starting with treatment B (TTS-F + DEX). In the prevention of acute N&V, the overall efficacy of OND + DEX was statistically significantly higher than that of TTS-F + DEX in achieving Complete Response (CR) and Major Efficacy (ME = CR + Major Response, MaR). As for delayed N&V, the overall efficacy of M + DEX, both in achieving CR and ME, although higher, was statistically not significantly different from that of TTS-F + DEX. Unfortunately, due to the small number of patients included in the study, the sophisticated criteria for evaluating response in antiemetic research, such as the persistence of efficacy, the response after crossing-over, did not make it possible for us to draw additional conclusions, although the trend was in favor of "standard" treatments, particularly in acute N&V. The 'response to treatment A (OND + DEX) in the prevention of acute N&V was in the same range as the response to treatment A (M + DEX) for delayed N&V. The response to treatment B (TTS-F) for acute N&V was lower than the response to the same treatment for delayed N&V. The TTS-F treatment was well-tolerated with no significant side-effects including the well-known opioid-related symptoms. Our study confirms that the currently available standard antiemetic treatments both for acute and delayed N&V must be considered by far the most effective ones for clinical use.
Department of Medical Oncology, University of Cagliari, Italy.
mantovan@pacs.unica.it

- McNamara P (2002). Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care. *Palliat Med* **16**:425–34. Summary: The study objective was to determine whether switching patients from morphine to transdermal fentanyl resulted in a reduction of morphine-associated side effects, and an improvement in cognitive function and patients' well being while maintaining adequate pain and symptom control. Nineteen patients aged 42–86 with terminal cancer, maintained on morphine for pain and distressed as a result of morphine toxicity, were given the dose of fentanyl corresponding to their current morphine dose. Pain control was then maintained (mostly fentanyl 50–100 microg/h) over the 14-day study period. Throughout the study, patients' global assessment of well being (primary efficacy variable) was statistically significantly improved. Sleepiness and drowsiness were significantly less of a problem. There was a trend towards improvement in attention span/concentration, and in the power and quality of concentration. Cognitive function tests also revealed a significant improvement in working (short term) and speed of memory although not in secondary (long term) memory. Patients did not experience hallucinations or delusions and there was no change in levels of anxiety

or depression (Hospital Anxiety Depression Scale). The incidence of dizziness was significantly reduced, and there was a nonsignificant decrease in number of patients who suffered myoclonus and in the severity of this condition over the 14 days. The investigator's overall impression of treatment with transdermal fentanyl was 'fair', which was not in agreement with the positive impression expressed by patients (score 74, range: 0 worst, 100 best). Further work is required to determine if the improvement in patients' well being and cognitive function is achieved in larger study populations. St. Oswald's Hospice, Gosforth, Newcastle-upon-Tyne, UK.

- Menten J, Desmedt M, Lossignol D and Mullie A (2002). Longitudinal follow-up of TTS-fentanyl use in patients with cancer-related pain: results of a compassionate-use study with special focus on elderly patients. *Curr Med Res Opin* **18**:488–98. Summary: GOALS OF THE WORK: This open compassionate-use prospective registration study evaluated the tolerability, ease of use and applied doses of transdermal (TTS) fentanyl in adult patients with cancer-related pain requiring strong opioid analgesia. Elderly patients were particularly focussed on. PATIENTS AND METHODS: Previous pain medication was converted to an appropriate dose of TTS-fentanyl. Immediate-release morphine rescue medication was allowed as needed for breakthrough pain. Dose adjustments of TTS-fentanyl, rescue morphine requirements, the ease of use and side-effects were assessed monthly, with special emphasis paid to the severity of constipation and the use of laxatives. MAIN RESULTS: A total of 663 patients with cancer-related pain, including 8% opioid-naive patients, were enrolled; 661 patients used at least 1 patch of TTS-fentanyl. Of these, 455 subjects were assessed at baseline and at 1 post-baseline visit at least. Individual treatment ranged from a few days to 2 1/2 years; TTS-fentanyl doses ranged from 25 to 950 microg/h. The major reason for study termination was non-drug-related death (61%). Approximately 40% of patients reported constipation. The frequency of constipation depended on the rescue morphine dose used, but no dose-relationship was found for TTS-fentanyl. Patient acceptance of the patches was high; around 85% of patients rated convenience as good to excellent. The ease of use and tolerability of TTS-fentanyl in the elderly patients were comparable to that in the total population, except for a slight increase of non-serious adverse events. CONCLUSIONS: TTS-fentanyl can be applied as long-term therapy to patients with cancer-related pain, including the elderly. University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Johan.Menten@uz.kuleuven.ac.be

- Muijsers RB and Wagstaff AJ (2001). Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* **61**:2289–307. Summary: Fentanyl is a

synthetic opioid agonist which interacts primarily with the mu-opioid receptor. The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery by the transdermal therapeutic system. These patches are designed to deliver fentanyl at a constant rate (25, 50, 75 and 100 microg/h), and require replacement every 3 days. Data from randomised, nonblind trials suggest that transdermal fentanyl is as effective as sustained-release oral morphine in the treatment of chronic cancer pain, as reported by patients using visual and numerical analogue scales as well as verbal description scales. No obvious differences in health-related quality of life were found in patients with chronic cancer pain when comparing transdermal fentanyl with sustained-release oral morphine. Nevertheless, significantly more patients expressed a preference for transdermal fentanyl than for sustained-release oral morphine after a randomised, nonblind, crossover trial. Because of the formation of a fentanyl depot in the skin tissue, serum fentanyl concentrations increase gradually following initial application, generally levelling off between 12 and 24 hours. Thereafter, they remain relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Once achieved, steady-state plasma fentanyl concentrations can be maintained for as long as the patches are renewed. The most frequently observed adverse events during transdermal fentanyl administration (as with other opioid agonists) included vomiting, nausea and constipation. Data from a nonblind, randomised trials suggest that constipation occurs less frequently in patients receiving transdermal fentanyl than in those given sustained-release oral morphine. The most serious adverse event reported in US premarketing trials was hypoventilation, which occurred with an incidence of approximately 2%. Adverse reactions related to skin and appendages (i.e. rash and application site reactions – erythema, papules, itching and oedema) were reported in 153 patients with cancer at a frequency between 1 and 3%. **CONCLUSION:** Transdermal fentanyl is a useful opioid-agonist for the treatment of moderate to severe chronic cancer pain. The advantages of transdermal fentanyl include ease of administration and the 3-day application interval. These factors coupled with a lower incidence of constipation are likely to contribute to the reported patient preference of transdermal fentanyl over sustained-release oral morphine. Adis International Limited, Auckland, New Zealand. demail@adis.co.nz

- Murphy M and Carmichael AJ (2000). Transdermal drug delivery systems and skin sensitivity reactions. Incidence and management. *Am J Clin Dermatol* 1:361–8. Summary: Transdermal devices are now marketed for the delivery of systemic medication through the skin. Advantages associated with transdermal drug delivery include avoidance of first-pass metabolism and variable absorption as well as improved patient

compliance. Drugs currently available by this route include scopolamine, nitroglycerin (glyceryl trinitrate), estradiol, nicotine, clonidine, fentanyl, and testosterone. This novel development has brought about a specific constellation of skin problems which vary widely in incidence between drugs. It is important to vary the site of drug administration to minimize these reactions. Any eczematous reaction can be treated with a moderately potent topical corticosteroid. Patients with topical sensitivity are usually tolerant of oral challenge but systemic sensitization has been reported and caution is still advocated before proceeding to this step. The increasing use of transdermal drug delivery systems across many specialities means that problems of skin sensitivity are of growing relevance to the dermatologist, the hospital specialist, and the primary care physician. Department of Dermatology, South Cleveland Hospital, Middlesbrough, England.

- Mystakidou K, Befon S, Kouskouni E, Gerolymatos K, Georgaki S, Tsilika E and Vlahos L (2001). From codeine to transdermal fentanyl for cancer pain control: a safety and efficacy clinical trial. *Anticancer Res* **21**:2225–30. Summary: BACKGROUND: Fentanyl is a synthetic opioid, suitable for transdermal delivery, offering an interesting solution as a step 3 opioid in cancer pain treatment. The purpose of the study was to carefully investigate: 1) the feasibility of the direct conversion from codeine to TTS fentanyl, in patients already receiving codeine and requiring strong opioids for their analgesia; 2) the safety of 25 microg/hour incremental steps and at shorter than 72-hour intervals, if clinically required. PATIENTS AND METHODS: 130 patients were judged eligible for the study. All the patients were receiving 280–360 mg or more of codeine and required strong opioid for their analgesia. The study lasted 56 days. The initial dose was 25 microg/hour. TTS fentanyl for all patients. Data assessments were made on baseline, day 1, day 2, day 3, in the hospital and thereafter on days 7, 14, 21, 28, 42 and 56. After the patch application, all the patients were given an immediate release oral morphine (5 mg) every 4–6 hours for the first 12 hours and then if needed only as rescue doses. The patients remained in the hospital for the first three days of the study where follow-up (pain score, satisfaction, side effects etc.) was recorded by the palliative care team and by daily cards. RESULTS: The initial dose of fentanyl was 25 microg/hour while the mean dose on day 3 was 45.9 microg/hour. All the patients required upward titration of the study medication during follow-up visits. On day 56 the mean dose of fentanyl was 87.4 microg/hour. Mean pain intensity decreased from an initial 5.96 on the baseline to 0.83 on day 3. Karnofsky scale measurements between treatment phases revealed non-significant changes. The rate of overall satisfaction was quite high. Nine patients discontinued the study due to inadequate pain relief or side effects between day 7 and day 28, while five patients died between day

28 and day 56. Constipation, nausea and vomiting were the most common side effects. Skin reaction was relatively mild and acceptable during the study. CONCLUSION: Under controlled conditions, TTS fentanyl seems to be feasible for direct conversion from mild to strong opioids and additionally, 25 microg/hour incremental steps day by day can be made by palliative care specialists, if clinically required for cancer pain management. Pain Relief and Palliative Care Unit, Areteion Hospital, University of Athens, Greece.

- Neighbors DM, Bell TJ, Wilson J and Dodd SL (2001). Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain. *J Pain Symptom Manage* **21**:129–43. Summary: The fentanyl transdermal system (Duragesic) is an opioid analgesic indicated for the management of chronic moderate to severe pain. The purpose of this analysis is to estimate its economic value compared to two long-acting oral opioids. A cost-utility analysis was performed using a three-phased decision analytic model. The transdermal system had the highest expected cost during the first year of therapy (\$2,491), moderately higher than the cost of a year of therapy with controlled-release morphine (\$2,037) or controlled-release oxycodone (\$2,307). The system also had the highest expected number of quality-adjusted life-days (QALDs) (244 compared to 236 for morphine and 231 for oxycodone), despite conservative assumptions. The fentanyl transdermal system achieved incremental cost-utility ratios of \$20,709 (vs. morphine) and \$5,273 (vs. oxycodone) per quality-adjusted life year (QALY) gained. In a conservative modeled analysis, the fentanyl transdermal system led to increased QALDs at a nominal increased cost. In the absence of head-to-head clinical trials, models help clarify cost and outcome trade-offs and provide a consistent theoretical framework for use by individual decisionmakers. Research Triangle Institute, Research Triangle, NC 27709, USA.
- Newshan G (1998). Heat-related toxicity with the fentanyl transdermal patch. *J Pain Symptom Manage* **16**:277–8. Summary:
- Noyes M and Irving H (2001). The use of transdermal fentanyl in pediatric oncology palliative care. *Am J Hosp Palliat Care* **18**:411–6. Summary: Transdermal fentanyl offers a noninvasive approach to the management of patients with opioid dependent and stable, chronic cancer pain. The transdermal delivery system offers distinct advantages where oral administration of opioids is difficult as a consequence of progressive disease and in patients whose compliance with oral medications is poor. Thirteen patients ranging in age from three years and nine months to 18 years and seven months were treated with transdermal fentanyl for between six hours and 112 days. All had

previously been receiving oral morphine prior to the commencement of fentanyl and were transferred to fentanyl because of oral opioid side effects and poor oral compliance. Fentanyl was well tolerated and provided effective pain relief for 11 of 13 patients. Overall, patients and parents experienced satisfaction with fentanyl, both in terms of pain relief and improvement in quality of life. Haematology and Oncology Unit, Royal Children's Hospital, Brisbane, Queensland, Australia.

- Nugent M, Davis C, Brooks D and Ahmedzai SH (2001). Long-term observations of patients receiving transdermal fentanyl after a randomized trial. *J Pain Symptom Manage* 21:385–91. Summary: We observed 73 cancer patients receiving transdermal fentanyl for 1–29 (mean 5.5) months immediately after participation in a randomized clinical trial. Of these, 32 received fentanyl until death, 18 were lost to follow-up, 11 required alternative analgesia, and 12 withdrew for other reasons. The median first recorded dose (not necessarily the patient's first fentanyl dose) was 75 microg/h. The median final dose was 100 microg/h. All but 3 patients required <300 microg fentanyl/h. In the 16 who received fentanyl for > or =3 months until death, the median dose was unchanged (100 microg/h) 3 months before death and at death; 8/16 required no dosage change. The incidence of constipation, skin reactions, nausea, and vomiting was low. No significant respiratory depression was associated with fentanyl. Most patients (85%) and investigators (86%) rated the treatment as good or excellent. We conclude that long-term treatment with transdermal fentanyl is safe and acceptable to many cancer patients. St. Luke's Hospice, Plymouth, United Kingdom.

- Pandey CK, Bose N, Garg G, Singh N, Baronia A, Agarwal A, Singh PK and Singh U (2002). Gabapentin for the treatment of pain in guillain-barre syndrome: a double-blinded, placebo-controlled, crossover study. *Anesth Analg* 95:1719–23, table of contents. Summary: Pain syndromes of Guillain-Barre are neuropathic as well as nociceptive in origin. We aimed to evaluate the therapeutic efficacy of gabapentin in relieving the bimodal nature of pain in Guillain-Barre syndrome in a randomized, double-blinded, placebo-controlled, crossover study in 18 patients admitted to the intensive care unit for ventilatory support. Patients were assigned to receive either gabapentin (15 mg. kg⁻¹. d⁻¹ in 3 divided doses) or matching placebo as initial medication for 7 days. After a 2-day washout period, those who previously received gabapentin received placebo, and those previously receiving placebo received gabapentin as in the initial phase. Fentanyl 2 micro g/kg was used as a rescue analgesic on patient demand or when the pain score was >5 on a numeric rating scale of 0–10. The numeric rating score, sedation score, consumption of fentanyl, and adverse effects were noted, and these observed variables

were compared. The numeric pain score decreased from 7.22 +/- 0.83 to 2.33 +/- 1.67 on the second day after initiation of gabapentin therapy and remained low during the period of gabapentin therapy (2.06 +/- 0.63) (P < 0.001). There was a significant decrease in the need for fentanyl from Day 1 to Day 7 during the gabapentin therapy period (211.11 +/- 21.39 to 65.53 +/- 16.17 [micro g]) in comparison to the placebo therapy period (319.44 +/- 25.08 to 316.67 +/- 24.25 [micro g]) (P < 0.001). IMPLICATIONS: Gabapentin, an antiepileptic drug, has been used effectively for different types of pain management. This study demonstrates that gabapentin has minimal side effects and is an alternative to opioids and nonsteroidal antiinflammatory drugs for management of the bimodal nature of pain of Guillain–Barre Syndrome patients. Department of Anaesthesiology and Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India. ckpandey@sippi.ac.in

- Parran L and Pederson C (2002). Effects of an opioid taper algorithm in hematopoietic progenitor cell transplant recipients. *Oncol Nurs Forum* 29:41–50. Summary: PURPOSE/OBJECTIVES: To examine the effects of an opioid taper algorithm on the length of taper, pain levels, withdrawal symptoms, and satisfaction with pain management in hematopoietic progenitor cell transplant (HPCT) recipients and nurse documentation of patient response to taper. DESIGN: Quasi–experimental. SETTING: A 32–bed HPCT unit in a large tertiary U.S. healthcare center. SAMPLE: 106 HPCT recipients, 5–64 years of age. METHODS: In phase 1, baseline data were collected from 45 patients during opioid tapers, with no study intervention. In phase 2, an opioid taper algorithm was implemented as the study intervention for 61 patients. MAIN RESEARCH VARIABLES: Phase 1 and phase 2 pretaper and taper opioid dosage, length of taper, nurse documentation, patient–reported pain and withdrawal symptoms, and nurses' perspectives about the use of tapers. FINDINGS: Use of the algorithm in phase 2 resulted in decreasing taper time by a mean of 0.4 days, a significant decrease in withdrawal symptoms, a significant increase in only 1 of 10 aspects of nurse documentation, and no significant differences in patient self–reports of worst pain or satisfaction with pain management. Nausea, vomiting, diarrhea, insomnia, and runny nose were the withdrawal symptoms reported most frequently. CONCLUSIONS: Use of the algorithm improved tapering practice somewhat without disadvantaging patients. IMPLICATIONS FOR NURSING PRACTICE: Use of an opioid taper algorithm may promote consistency of tapering practice. Fairview–University Medical Center, Minneapolis, MN, USA. lparran1@fairview.org

- Paut O, Camboulives J, Viard L, Lemoing JP and Levron JC (2000). Pharmacokinetics of transdermal fentanyl in the peri–operative period in

young children. *Anaesthesia* 55:1202–7. Summary: The pharmacokinetics of transdermal fentanyl were assessed in eight children aged 18–60 months, weighing 11–20 kg and monitored postoperatively in the intensive care unit. A patch, delivering 25 microg.h⁻¹ of fentanyl, was applied for 72 h from the induction of anaesthesia. Plasma fentanyl concentrations were measured over 144 h. Mean (SD) peak concentration of fentanyl was 1.7 (0.66) ng.ml⁻¹ and time to reach maximal plasma concentration was 18 (11) h. The elimination half-life was 14.5 (6.2) h, and the area under the curve for plasma fentanyl concentration (0–144 h) was 86.8 (27) ng.h.ml⁻¹. Maximal fentanyl concentration was negatively correlated with patient age ($r = -0.71$; $p = 0.049$) but not with body weight. These results suggest that the pharmacokinetics of transdermal fentanyl in children are similar to those in adults. Staff Anaesthetist and Professor of Anaesthesia and Director of Anaesthesia Department, Department of Paediatric Anaesthesia and Intensive Care, La Timone University Hospital, Bd Jean Moulin, 13385 Marseilles cedex 5, France; Researcher and Dir.

- Payne R (1998). Factors influencing quality of life in cancer patients: the role of transdermal fentanyl in the management of pain. *Semin Oncol* 25:47–53. Summary: A transdermal fentanyl patch for the treatment of chronic cancer-related pain is available in four dosages (25, 50, 75, and 100 microg/hr). Fentanyl is released from a 72-hour reservoir by diffusion through a controlled-release membrane to the skin, through which it is absorbed into the microcirculation. The pharmacokinetics of fentanyl differ markedly as a function of the route of administration. Unlike intravenous administration, in which peak plasma levels occur within minutes and the plasma elimination half-life is 2 to 3 hours, after initial transdermal fentanyl patch application, peak levels occur within 14 hours and the elimination half-life exceeds 24 hours. When compared with oral morphine at doses effecting the same degree of pain relief, fewer gastrointestinal disturbances (nausea, vomiting, and constipation) and better alertness and sleep quality have been reported in two studies. The transdermal fentanyl patch is as effective as oral opioids in relieving cancer-related pain, with a safety and side effect profile equal to or better than that of oral opioids. The convenient, once-every-72 hours dosing regimen is easily adjusted to the individual's need for around-the-clock pain control, and provides stable and predictable therapeutic drug plasma concentrations. Patient acceptability is high and the cost is lower than other methods required to deliver parenteral opioids. The recent development of an oral transmucosal fentanyl citrate delivery system for the treatment of breakthrough pain will further expand the use of transdermal fentanyl patches for the treatment of chronic pain. Department of Neuro-Oncology, M.D. Anderson Cancer Center, Houston, TX, USA.

- Payne R, Mathias SD, Pasta DJ, Wanke LA, Williams R and Mahmoud R (1998). Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. *J Clin Oncol* **16**:1588–93. Summary: PURPOSE: To compare pain-related treatment satisfaction, patient-perceived side effects, functioning, and well-being in patients with advanced cancer who were receiving either transdermal fentanyl (Duragesic, Janssen Pharmaceuticals, Titusville, NJ) or sustained-release oral forms of morphine (MS Contin, Perdue Frederick Co, Norwalk, CT, or Oramorph SR, Roxanne Laboratories, Columbus, OH). PATIENTS AND METHODS: A total of 504 assessable cancer patients participated in this cross-sectional, quality-of-life study. Relevant elements of four validated scales were used--the Functional Assessment of Cancer Therapy-General (FACT-G) scale, the Brief Pain Inventory (BPI), the Medical Outcomes Study (MOS) questionnaire, and the Memorial Symptom Assessment Scale (MSAS)--as well as original scales that were developed and validated for this study. RESULTS: The majority of patients in both treatment groups had late-stage (IV/D) cancer. Patients who received transdermal fentanyl were more satisfied overall with their pain medication than those who received sustained-release oral forms of morphine ($P = .035$). Fentanyl patients also experienced a significantly lower frequency ($P < .002$) and impact ($P < .001$) of pain medication side effects. These results occurred despite the fact that cancer patients who received fentanyl were significantly older ($P < .001$) and had significantly lower functioning and well-being scores ($P = .001$). Measures of pain intensity, sleep adequacy, and symptoms demonstrated no significant differences between treatment groups. CONCLUSION: These data suggest that patients are more satisfied with transdermal fentanyl compared with sustained-release oral forms of morphine. A lower frequency and reduced impact of side effects with transdermal fentanyl may be one reason cancer patients who receive fentanyl are more satisfied with their pain management. University of Texas M.D. Anderson Cancer Center, Houston 77030, USA. rp@mdanderson.com

- Purucker M and Swann W (2000). Potential for duragesic patch abuse. *Ann Emerg Med* **35**:314. Summary:

- Radbruch L, Sabatowski R, Elsner F, Loick G and Kohnen N (2002). Patients' associations with regard to analgesic drugs and their forms for application -- a pilot study. *Support Care Cancer* **10**:480–5. Summary: Patients' and caregivers' fear of addiction to and concern about side effects of morphine have been found to be among the major barriers to adequate pain relief in cancer patients. In contrast, the transdermal administration of opioids by means of fentanyl patches does not seem to evoke such fears. In a qualitative study, 60 patients in our outpatient pain

clinic recorded up to five associations with a list of diseases, drugs and administration routes. Cancer and AIDS were associated most often with death, followed by suffering, anxiety and hopelessness. Migraine was associated predominantly with pain and other physical symptoms. Aspirin was associated less with pain in general than with headache and, sometimes, specifically with alcohol or hangover. Morphine was associated predominantly with pain and pain relief, but fears of intoxication, abuse and addiction and concerns about side effects were frequently named. Major differences were evident from the associations with the different routes of administration. The word 'pill' was mostly associated with contraception. Associations with 'tablets' were more pharmacological in nature, and side effects were frequently named. Patches were associated with wounds, cuts, bruises, and blisters and with protection. Some associations with patches were related to comfort. Injections and infusions were associated with physicians or the hospital environment. In conclusion, patients expressed major differences in their perceptions of the different drugs and routes of administration. The results may give a first hint that minor cultural differences even between western European countries may lead to major differences in prescribing habits and treatment regimens. Department of Anaesthesiology, University of Cologne, Cologne, Germany. Lukas.Radbruch@uni-koeln.de

- Radbruch L, Sabatowski R, Loick G, Brunsch–Radbruch A and Lehmann KA (1999). [WHO recommendations for treatment of tumor pain. Development of an evaluation system]. *Schmerz* 13:259–65. Summary: AIM OF THE STUDY: Evaluation of the observance of the World Health Organization guidelines for cancer pain management is a prerequisite for further research into the effectiveness and acceptability of the guidelines. METHODS: In a nationwide survey 172 physicians in pain management and oncological units documented transdermal therapy with fentanyl. From October 1996 to May 1997, 591 patients were included. A total of 148 patients had already received transdermal fentanyl before inclusion in the survey, and no data on previous analgesic management were available for 7 patients. For 436 patients analgesic therapy before initiation of transdermal fentanyl was evaluated. The last analgesic regimen documented by the treating physician was rated by three physicians from our pain clinic independently of each other. A rating system with four items (potency of analgesic according to the analgesic ladder of the WHO guidelines, prescription of a rescue medication, combination of nonopioids with opioids, inadequate combinations of analgesics) and a global rating (the analgesic regimen is considered adequate, sufficient or inadequate) was used. RESULTS: Good agreement was reached for classification according to the analgesic ladder, prescription of rescue medication and for inadequate drug combinations. The ratings on combinations with nonopioids showed more differences.

The scores for the global assessment showed a wide difference between raters, with agreement on the same score for only 36.2% (raters 1 and 3), 36.7% (raters 2 and 3) and 55.5% of the patients (raters 1 and 3).

CONCLUSIONS: A global assessment score is not useful for evaluation of guideline acceptance. A more differentiated scoring system was developed for further studies that includes the analgesic ladder and other aspects of the WHO guidelines in a 10-point score. Klinik und Poliklinik für Anesthesiologie und Operative Intensivmedizin, Universität Köln.

- Radbruch L, Sabatowski R, Petzke F, Brunsch-Radbruch A, Grond S and Lehmann KA (2001). Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med* 15:309–21. Summary: Transdermal fentanyl was released in Germany in 1995. From October 1996 to February 1998 transdermal treatment was documented for 1005 patients (506 men and 499 women with a mean age of 60 years, range 20–92 years) with chronic pain in an open survey including 290 physicians from hospitals and general practitioners throughout Germany. Most patients suffered from cancer pain and only 11 patients had chronic pain from non-malignant disease. Physicians were asked to complete a questionnaire for patients treated with transdermal fentanyl on initiation of therapy (day 0), and days 3, 6, 18, 30 thereafter, followed by monthly follow-up intervals. Patients were asked to complete a pain diary. Transdermal therapy was documented from day 0 for 824 patients, while 181 patients had been treated with transdermal fentanyl before admission in the survey. Most of the other 824 patients had been treated with other step 3 opioids (55% of the patients) or step 2 opioids (23%) before conversion to transdermal fentanyl, whereas 8% had been treated only with non-opioids and 14% had received analgesics only as required or not at all before initiation of transdermal therapy. The most important reasons for switching to transdermal opioid therapy were insufficient pain relief with the previous medication followed by a variety of gastrointestinal symptoms impeding oral analgesic therapy. Initial fentanyl doses ranged from 0.6 to 9.6 mg/day (25 to 400 microg/h) with a median of 1.2 mg/day (50 microg/h). Median doses slowly increased throughout the observation period to 2.4 mg/day (100 microg/h) after 4 months of treatment. Most patients continued transdermal therapy until the time of death (47% of patients). Other reasons for discontinuation were inadequate pain relief (10%), pain relief with other analgesic regimens (10%), other symptoms than pain (5%), rejection of transdermal therapy by the patient (6%) or miscellaneous (16%). Adverse events were documented as the reason for discontinuation of transdermal therapy in 49 patients (5%). Dyspnoea was documented for seven patients as the reason for discontinuation. One of these patients, as well as another patient with an episode of apnoea, had to be treated with artificial respiration for several hours, but both patients recovered without

sequelae. Transdermal therapy with fentanyl was safe and efficient in this national survey. Transdermal fentanyl can be recommended for treatment of moderate to severe cancer pain and probably may even be used as a first-line drug on step 3 of the World Health Organization recommendations in selected patient groups. Department of Anaesthesiology, University of Cologne, Germany. lukas.radbruch@uni-koeln.de

- Reeves MD and Ginifer CJ (2002). Fatal intravenous misuse of transdermal fentanyl. *Med J Aust* **177**:552–3. Summary: The introduction of a transdermal delivery system for fentanyl means that it is now more readily available. We present the first documented fatality after intravenous injection of the contents of a transdermal fentanyl patch. Prescribers need to be aware of the potential for misuse of fentanyl patches. Department of Anaesthesia, North West Regional Hospital, Burnie, TAS, Australia.
- Ringe JD, Faber H, Bock O, Valentine S, Felsenberg D, Pfeifer M, Minne HW and Schwalen S (2002). Transdermal fentanyl for the treatment of back pain caused by vertebral osteoporosis. *Rheumatol Int* **22**:199–203. Summary: Pain relief for patients with osteoporosis is important to maintain mobility and facilitate physical therapy. Transdermal fentanyl may be useful but has not been studied systematically. Patients with at least one osteoporotic vertebral fracture requiring strong opioids were enrolled and received transdermal fentanyl. Treatment history, pain, ease of physical therapy, and quality of life were recorded at baseline and after 4 weeks. Of 64 patients enrolled, 49 completed the study; 12 withdrew because of adverse events, most commonly nausea, vomiting, or dizziness. Pain at rest and on movement decreased significantly from baseline to final assessment (mean scores 7.84 and 8.55, respectively, at baseline, falling to 3.56 and 4.50 after 4 weeks). Quality of life improved significantly, and 61% of patients were satisfied with the treatment. Ability to undergo physical therapy improved significantly. Transdermal fentanyl is useful for the treatment of severe back pain caused by osteoporosis. Medizinische Klinik 4, Klinikum Leverkusen, Dhuennberg 60, 51375 Leverkusen, Germany. ringe@klinikum-lev.de
- Robards M (2001). Transdermal fentanyl in the hospice: a survey of rescue dosing and pain control. *Am J Hosp Palliat Care* **18**:47–50. Summary: The case records of 25 patients who received transdermal fentanyl as a primary analgesic during routine hospice care were surveyed for pain control and rescue medication use. The majority of patients (76 percent) had cancer-related pain and were treated in hospice for an average of approximately 30 days. Most received oral medications for supplemental rescue analgesia. During the sampling periods, on average,

pain intensity was reported as mild. Over the same periods, patients required a mean of 6.1 (+/- 0.7) doses of rescue medication per day, with a range of zero to 12 doses per day. Five patients required rescue dosing every two hours on some treatment days. Although adequate pain control was generally accomplished with transdermal fentanyl in the group as a whole, the frequency of rescue dosing outside of the initial titration period appears unacceptably high. Visiting Nurse Association Hospice Care, St. Louis, Missouri, USA.

- Roberge RJ, Krenzelok EP and Mrvos R (2000). Transdermal drug delivery system exposure outcomes. *J Emerg Med* **18**:147–51. Summary: Transdermal drug delivery systems are increasingly popular, yet few data exist regarding medical outcomes after exposures. Using data collected through a Regional Poison Information System, this retrospective study identified 61 cases of transdermal drug delivery system exposures reported over a recent 5-year period. Exposure routes included dermal (48 patients), oral (10 patients), combined oral and dermal (one patient), parenteral use of gel residue (one patient), and combined oral and parenteral (one patient). Forty-four exposures (72%) were managed by home telephone consultation only. Eleven of 17 patients (18%) evaluated in health care facilities were admitted, including eight (13%) to intensive care units. Hospital admission correlated statistically with clonidine and fentanyl exposures, oral exposures, and drug abuse. Clonidine exposure also correlated statistically with intensive care admission. One fatality was recorded, and all other patients recovered uneventfully. Transdermal drug delivery system exposures are infrequently reported to our regional poison information center but are associated with a significant hospital use and admission rate. Department of Emergency Medicine, Western Pennsylvania Hospital, Pittsburgh 15224, USA.

- Roth JV (2002). Warming blankets should not be placed over transdermal medications. *Anesth Analg* **94**:1043. Summary:

- Sabatowski R, Arens ER, Waap I and Radbruch L (2001). [Cancer pain management in Germany – results and analysis of a questionnaire]. *Schmerz* **15**:241–7. Summary: The German regulations for opioid prescriptions have been changed in February 1998. The regulations have been made much more easier and should therefore have improved the pain management in Germany. We investigated the knowledge of the WHO analgesic ladder and how they have been followed in a nation-wide survey among physicians not specialised in pain management. Only 9% of the questionnaires were returned. Although the majority of the physicians (93%) reported knowledge about the WHO recommendations for the treatment of cancer pain, more than 15% of the participating physicians rated transdermal fentanyl as a weak opioid or even as a non-opioid. A

negative pain management index in 15% of the patients gave evidence of poor quality in pain management. The majority of patients (84%) did not receive immediate release analgesics for the treatment of breakthrough pain. Continuous medical education is still necessary before a further alleviation of regulations will help to reduce the undertreatment of patients suffering from cancer pain in Germany. Klinik und Poliklinik für Anesthesiologie und Operative Intensivmedizin, Universität zu Köln. rainer.sabatowski@uni-koeln.de

- Sabatowski R, Schwalen S, Rettig K, Herberg KW, Kasper SM and Radbruch L (2003). Driving ability under long-term treatment with transdermal fentanyl. *J Pain Symptom Manage* 25:38–47. Summary: Clinical experience shows that neuropsychological side effects due to opioid therapy usually decrease during the first weeks of therapy. However, the effect of long-term treatment with transdermal fentanyl on complex activities, such as driving, is not yet clear. In a prospective trial, patients with continuous noncancer pain, who had received stable doses of transdermal fentanyl for at least 2 weeks, completed a series of computerized tests to measure attention, reaction, visual orientation, motor coordination and vigilance. Data from 90 healthy volunteers were matched to 30 patients; 9 patients were excluded from the per-protocol analysis because they took additional drugs in violation of the protocol. None of the performance measures for the 21 remaining fentanyl patients was significantly inferior to the controls. We conclude that stable doses of transdermal fentanyl for the treatment of chronic non-cancer pain are not associated with significant impairments in psychomotor and cognitive performance. The threshold for fitness to drive as defined by German law did not differ significantly between the groups. Department of Anesthesiology, University of Cologne, Cologne, Germany.
- Simpson RK, Jr., Edmondson EA, Constant CF and Collier C (1997). Transdermal fentanyl as treatment for chronic low back pain. *J Pain Symptom Manage* 14:218–24. Summary: Management of chronic low back pain often includes oral opioid use. The effectiveness of therapy is dependent upon compliance, which in turn is dependent upon response, side effects, access, and convenience. Our hypothesis was that a transdermal fentanyl system would provide more effective pain management than oral opioids. Fifty patients with chronic low back pain were examined. After titration to levels corresponding to current oral opioid use, each patient was maintained on transdermal fentanyl for one month. Oral opioid therapy was then resumed. Their experience was assessed with the a visual analogue scale for pain intensity, a numerical pain score, the Oswestry disability questionnaire, the pain disability index, and the Verran Snyder–Halpern sleep scale. Significant improvement in pain relief and disability was found with transdermal

fentanyl compared with oral opioids. Mild opioid side effects were common, but easily controlled. Use of transdermal fentanyl is an effective alternative to oral opioids for managing chronic low back pain.

Department of Neurosurgery, Baylor College of Medicine, Houston, Texas 77030, USA.

- Sloan PA, Moulin DE and Hays H (1998). A clinical evaluation of transdermal therapeutic system fentanyl for the treatment of cancer pain. *J Pain Symptom Manage* **16**:102–11. Summary: Fentanyl has been incorporated into a transdermal therapeutic system (TTS) containing a rate-limiting membrane that provides constant release of the opioid. TTS fentanyl provides continuous opioid delivery for up to 72 hr without the need for special equipment. After Institutional Review Board approval, 53 patients with cancer pain requiring 45 mg or more of oral morphine daily were admitted into an open-label, prospective, multicenter evaluation of TTS fentanyl for the relief of pain. After a 1-week stabilization on oral morphine, patients were transferred from morphine to an appropriate dose of TTS-fentanyl (25, 50, 75, or 100 micrograms/hr) administered as a transdermal patch every 3 days. TTS fentanyl was titrated to pain relief, and patients were followed up for as long as 3 months. Pain relief and the side effects of the medications were assessed daily. Twenty-six men and 27 women with a mean (\pm SD) age of 61 (\pm 12) years entered the study; 23 patients completed the full 84-day study. The mean duration of TTS fentanyl use was 58 \pm 32 days. The mean (\pm SEM) daily morphine dose during the last 2 days of stabilization was 189 (\pm 20) mg, and the mean initial fentanyl patch dose was 58 (\pm 6) micrograms/hr. The mean daily morphine dose taken "as needed" for breakthrough pain at study completion was 35 mg. The mean final fentanyl dosage at study completion was 169 (\pm 29) micrograms/hr. Pain relief was rated as good or excellent by 82% of patients during the treatment period. When asked to compare pain relief during the first month of TTS-fentanyl use to that provided by their last analgesic before study entry, 63% preferred TTS fentanyl. Side effects considered related to the fentanyl patch were nausea (13%), vomiting (8%), skin rash (8%), and drowsiness (4%). Thirty percent of patients reported adverse experiences related to the fentanyl patch, and 17% had to be discontinued from the study. We conclude that TTS fentanyl administered every 3 days for the treatment of cancer pain is effective, safe, and well tolerated by most patients. Department of Anesthesiology, University of Kentucky Hospital, Lexington 40536, USA.

- Sorensen J and Bengtsson M (1997). Intravenous phentolamine test--an aid in the evaluation of patients with persistent pain after low-back surgery? *Acta Anaesthesiol Scand* **41**:581–5. Summary: BACKGROUND: Persistent pain following surgery in the treatment of chronic low-back

pain patients is still relatively frequent. Most of these patients with persistent pain have clinical signs of neuropathic pain. The neuropathic pain might be sympathetically maintained pain (SMP) or sympathetically independent pain (SIP). Systemic administration of phentolamine, a competitive alpha-adrenergic antagonist, has been used as a diagnostic tool to identify patients with SMP. METHODS: Thirty-seven patients with persistent pain after low-back surgery (lumbar laminectomy, with or without discectomy, or a posterior fusion, with or without decompression) received intravenous phentolamine (0.5 mg/kg over 30 min) in a single-blind, placebo-controlled manner. Prior to this infusion the patients were classified clinically into different pain groups based on physical examination and imaging findings. An opioid epidural test blockade was used as a control. RESULTS: Clinical classification divided the patients into nociceptive pain (n = 7), neuropathic pain (n = 22) and mixed pain (n = 8). In the phentolamine test there were only one responder, 34 non-responders and 2 patients were placebo-responders. In the control epidural blockade there were 11 non-responders, 23 fentanyl/local anaesthetic-responders and 3 placebo-responders. CONCLUSIONS: SMP is either an uncommon cause of persistent pain in this type of failed back surgery patients or the phentolamine test, as we performed it, was unable to identify SMP. Department of Anesthesiology, University Hospital, Linköping, Sweden.

- Stevens M, Esler R and Asher G (2002). Transdermal fentanyl for the management of acute pancreatitis pain. *Appl Nurs Res* 15:102-10. Summary: Although the hazards of using Demerol for pain management is well documented, physicians at a 350-bed tertiary-care center in the upper midwest continued to follow the antiquated practice of ordering intramuscular Demerol and Vistaril to manage pain for patients with acute pancreatitis. Their reasoning was based on early evidence that Demerol, unlike morphine, does not cause biliary-tract spasms resulting in epigastric or right upper quadrant pain. In an effort to change practice patterns, a multidisciplinary team was formed to study the efficacy of using Transdermal Therapeutic System (TTS) fentanyl to manage pain in this patient population. Thirty-two subjects were enrolled in a double-blind, placebo-controlled study to evaluate the efficacy of using TTS fentanyl with intramuscular Demerol for breakthrough pain in comparison to using a placebo system and intramuscular Demerol. There was no statistically significant difference in self-reported pain intensity between the control and experimental groups on the first day of hospitalization. This finding would be expected because serum fentanyl concentrations rise gradually during the first 12 to 14 hours after application of the TTS fentanyl and plateau at 24 hours. There was a statistically significant difference between groups at 36 hours (exact $p < .0154$) and 45 hours (exact $p < .0132$) after application of the TTS fentanyl. This is probably

because of greater serum fentanyl concentrations observed during the 36- to 48-hour period after application of TTS fentanyl. Although not statistically significant, trends in the data revealed that the experimental group had lower self-reported pain intensity scores than the control group throughout the course of hospitalization. Even though the experimental group had significantly more previous hospitalizations for acute pancreatitis and a higher pain intensity score on admission, this group had a significantly shorter length of stay in the hospital $t(2, N = 31) = 4.3706$ $p < .05$. There was no statistically significant difference between the two groups for self-reported satisfaction with pain management. School of Nursing, Minnesota State University, Mankato 56001, USA. marcia.stevens@mankato.msus.edu

- Strumpf M, Linstedt U, Wiebalck A and Zenz M (2001). [Treatment of low back pain--significance, principles and danger]. *Schmerz* **15**:453-60. Summary: Today, a wide range of efficient analgesic and non-analgesic drugs for the treatment of back pain are available. However, drugs should never be the only mainstay of a back pain treatment program. Non-steroidal antiinflammatory drugs (NSAID) are widely used in acute back pain. NSAIDs prescribed at regular intervals are effective to reduce simple back pain. The different NSAIDs are effective for the reduction of this pain. They have serious adverse effects, particularly at high doses, in the elderly, and on long-term administration. The new cyclooxygenase II-inhibitors have less gastrointestinal complications. But the long-term experiences are limited up to now. Considerable controversy exists about the use of opioid analgesics in chronic noncancer pain. Many physicians are concerned about the effectiveness and adverse effects of opioids. Other clinicians argue that there is a role for opioid therapy in chronic noncancer pain, e. g. especially in chronic low back pain. There is a low incidence of organ toxicity in patients who respond to opioids. The incidence of abuse and addiction is likewise relatively low. The potential for increased function and improved quality of life seems to outweigh the risks. However, there is a lack of randomised controlled trials (RCT) on opioid therapy in a multimodal pain treatment approach. Clinical experience and some studies suggest administration of sustained release opioids because of better comfort for the patient and less risks for addiction. The opioids should be selected due to the specific side effects of the different drugs. For patients with pre-existing constipation transdermal fentanyl should be preferred. Antidepressant medications have been used for the treatment of chronic back pain, though there is only little scientific evidence for their effectiveness. There is no evidence for the use of antidepressants in acute low back pain. Trials of muscle relaxants for patients with acute back pain have used a wide range of agents, e. g. benzodiazepines. They mostly reduce acute back pain, but they have significant adverse effects including drowsiness and

psychological and physical dependence even after relatively short treatment. Benzodiazepines are not indicated in the treatment of chronic back pain. Drugs are sometimes necessary for the patients to begin and persevere a multimodal treatment program. Drug therapy should be terminated as soon as other treatment strategies succeed. Unfortunately, no studies exist evaluating the place of analgesics within a multimodal treatment program. BG-Universitätsklinikum Bergmannsheil, Bochum. strumpf@anaesthesia.de

- Thompson JP, Bower S, Liddle AM and Rowbotham DJ (1998). Perioperative pharmacokinetics of transdermal fentanyl in elderly and young adult patients. *Br J Anaesth* **81**:152–4. Summary: The perioperative pharmacokinetics of transdermally-delivered fentanyl were compared in 10 young adult (mean [range] age 32.7, [25–38] yr) and eight elderly (mean [range] age 73.7 [64–82] yr) patients following abdominal surgery. Transdermal fentanyl patches designed to release 50 micrograms h⁻¹ were applied 2 h preoperatively and left in place for 72 h. Plasma fentanyl concentrations were measured by radioimmunoassay during patch application and for 30 h after patch removal. The mean half-time (time for plasma concentrations to double after patch application) was 4.2 h in the younger group and 11.1 h in the elderly group ($P < 0.005$). Mean maximum plasma concentrations were 1.9 ng ml⁻¹ and 1.5 ng ml⁻¹ in the younger and elderly groups respectively (ns). There were no differences in the time at which maximum plasma concentrations occurred (t_{max}), elimination half-life after patch removal, or AUC(0–infinity). University Department of Anaesthesia, Leicester Royal Infirmary.
- Vanbever R, Langers G, Montmayeur S and Preat V (1998). Transdermal delivery of fentanyl: rapid onset of analgesia using skin electroporation. *J Control Release* **50**:225–35. Summary: Skin electroporation has recently been shown to increase transdermal transport of small-size drugs as well as considerably larger molecules by up to 4 orders of magnitude in vitro. Nevertheless, no in vivo studies have proven that high-voltage pulses can induce therapeutic plasma levels of drug. The aim of the present report was precisely to study the potential of skin electroporation in transdermal delivery of fentanyl in vivo. Fentanyl was transdermally delivered to hairless rats using high-voltage pulsing. Following the administration, the pharmacokinetics and pharmacodynamics were assessed. Significant fentanyl plasma concentrations were rapidly achieved using skin electroporation. Immediately after the 5 min pulsing, fentanyl plasma levels reached one third of the maximal plasma concentration of approximately 30 ng/ml, the peak occurring 30 min after the electroporation. Deep analgesia and supraspinal effects were achieved, antinociception lasting for an hour. The magnitude of the effects was, however, dependent on the electrical parameters of the pulses. *Unite de*

pharmacie galenique, Ecole de pharmacie, Universite catholique de Louvain, Brussels, Belgium.

- Vanbever R and Preat VV (1999). In vivo efficacy and safety of skin electroporation. *Adv Drug Deliv Rev* 35:77–88. Summary: This article reviews the studies on skin electroporation carried out in vivo in animals and emphasizes its potential therapeutic applications for transdermal and topical drug delivery. In agreement with in vitro studies, transport across skin due to high-voltage pulses in vivo was shown to increase by orders of magnitude on a timescale of minutes. Increased transdermal transport was measured by systemic blood uptake and/or pharmacological response, and demonstrated for calcein, a fluorescent tracer, fentanyl, a potent analgesic and flurbiprofen, an antiinflammatory drug. Combined electroporation with iontophoresis was shown to provide rapidly responsive transdermal transport of luteinizing hormone releasing hormone ex vivo as well. These data underline the potential of skin electroporation for improving the delivery profile of existing conventional transdermal patches, but also for replacing the injectable route. High-voltage pulses can increase drug permeation within and across skin but are also an efficient tool to permeabilize the membrane of cells of the cutaneous or subcutaneous tissue. This was shown beneficial for targeting cutaneous cells with oligonucleotides or genes and might open new opportunities for gene therapy and DNA vaccination. The safety of the application of high-voltage pulses on skin was assessed in vivo, using histological and visual scores, and bioengineering methods. While changes in skin barrier and function were observed, the irritation was mild and short-lived. Further optimization of the electrode configuration for improved targeting of the stratum corneum should still improve tolerance and levels of sensation. Department of Pharmaceutical Technology, School of Pharmacy, Catholic University of Louvain, Brussels, Belgium

- Vielvoye-Kerkmeer AP, Mattern C and Uitendaal MP (2000). Transdermal fentanyl in opioid-naive cancer pain patients: an open trial using transdermal fentanyl for the treatment of chronic cancer pain in opioid-naive patients and a group using codeine. *J Pain Symptom Manage* 19:185–92. Summary: To treat cancer pain, physicians often decide to jump directly from step 1 of the World Health Organization (WHO) analgesic ladder to step 3. The use of transdermal fentanyl in patients with cancer pain who had either used no opioid before, or only codeine, is evaluated in the present trial. Both opioid-naive (N = 14) and codeine-using (N = 14) patients started with transdermal fentanyl in the lowest available delivery rate (25 microg/hr). Immediate-release oral morphine was present as "rescue" medication. Transdermal fentanyl provided good to excellent pain relief in the majority (68%) of these patients. During the

study, 5 patients continued with 25 microg/hr, and the others used a higher dose. Clinically relevant respiratory depression was not observed. The common side effects of opioids were found; constipation was mentioned by 3 patients (11%). Transdermal fentanyl appeared a safe analgesic in these opioid-naïve cancer pain patients. In this study, WHO step 2 could be skipped without untoward complications. Department of Medical Oncology/Pain Team, The Netherlands Cancer Institute, Amsterdam.

- Woodroffe MA and Hays H (1997). Fentanyl transdermal system. Pain management at home. *Can Fam Physician* 43:268–72. Summary: PROBLEM BEING ADDRESSED: About 65% of patients with advanced malignancies experience cancer pain. Although oral opioids provide effective analgesia for most of these patients, alternate routes of drug delivery are often necessary as the disease progresses. PURPOSE OF PROGRAM: To study use of Duragesic (fentanyl transdermal system), the only transdermal opioid approved in Canada for treating chronic cancer pain in adults. MAIN COMPONENTS: Transdermal fentanyl was prescribed for a heterogeneous group of 44 patients (aged 29 to 82 years) to treat cancer pain (37 patients), chronic non-malignant pain (six patients), and pain associated with terminal AIDS (one patient), for periods of 2 to 384 days. Patients were treated individually and switched to transdermal fentanyl from other opioids when oral delivery was no longer possible. Doses were titrated as necessary and ranged from 25 micrograms/h to 300 micrograms/h. Incidental pain was treated effectively with short-acting opioids. CONCLUSIONS: Eighty percent of patients experienced good analgesia, which led to an overall improvement in their quality of life. Transdermal fentanyl was discontinued for 17% of patients due to intractable nausea, diarrhea, adherence problems, or poor analgesia. Many patients wore the system until they died or until a few days before death when severe increasing pain necessitated parenteral opioids. The side effects of transdermal fentanyl were similar to those of conventional opioids. Patient compliance and acceptance of this noninvasive, continuous system of drug delivery has been excellent; its simplicity of administration allows patients to be cared for at home. Department of Family Medicine, University of Alberta, Edmonton.

- Yeo W, Lam KK, Chan AT, Leung TW, Nip SY and Johnson PJ (1997). Transdermal fentanyl for severe cancer-related pain. *Palliat Med* 11:233–9. Summary: A prospective phase II study was conducted to define the analgesic efficacy, acceptability and toxicity of the transdermal therapeutic system (TTS) of fentanyl in Chinese patients with severe cancer-related pain. A total of 14 patients was treated with TTS fentanyl at doses ranging from 25 to 100 micrograms h⁻¹; initial doses were chosen according to their previous opioid requirement. Standard

supportive therapy was given as required. A brief pain inventory (using a 10-point scale) was used to assess patients at days 0, 7 and 14. Pain control on day 14 with TTS fentanyl was successful in six patients, with a reduction in the common side-effects of other opioids and improvement in general well-being. Seven patients did not complete the 14-day trial: two developed dizziness and nausea within 3 h of application; and in five, TTS fentanyl was insufficiently flexible to control increasing pain during the first week. TTS fentanyl was effective and well tolerated in 43% of patients. Acute dizziness and nausea within the first few hours after application and the relative inflexibility of dose-adjustment both limited the use of TTS fentanyl. Department of Clinical Oncology, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong.

- Zuurmond WW, Meert TF and Noorduyn H (2002). Partial versus full agonists for opioid-mediated analgesia--focus on fentanyl and buprenorphine. *Acta Anaesthesiol Belg* 53:193-201. Summary: In contrast to other opioids, fentanyl and buprenorphine share a number of physicochemical properties that render both agents potentially suitable for transdermal delivery. However, there are significant differences between them in terms of their pharmacological profiles, as fentanyl is a full mu opioid receptor agonist capable of exerting a maximal response in certain tissues, while buprenorphine is a partial agonist unable to exert this maximum effect even at high doses. This review examines the hypothesis that partial opioid agonists would confer a number of benefits over full agonists, namely effective analgesia with a better tolerability and a lower propensity for addiction, with respect to fentanyl and buprenorphine. An attempt is also made to correlate clinical differences between these drugs with their respective agonist profiles and other differential pharmacokinetic/pharmacodynamic properties. Despite a dearth of directly comparative trials, the pharmacology of fentanyl and buprenorphine is well documented. Considerable data concerning buprenorphine suggest that the advantages initially espoused for partial opioid agonists are not borne out in clinical practice. Indeed, it may be postulated that full mu opioid agonists, particularly those with high selectivity and potency such as fentanyl, have a superior clinical profile and fulfill the above criteria more closely. Relative receptor binding, selectivity, potency and intrinsic efficacy of the opioids appear to be key determinants of their individual pharmacological profiles, contributing significantly to the heterogeneity of this class of analgesics. Department of Anaesthesiology, Academic Hospital Vrije Universiteit, Postbus 7047, 1007 MB Amsterdam, The Netherlands. wwa.zuurmond@azvu.nl