Transdermal buprenorphine in cancer pain and palliative care

Reinhard Sittl

Palliat Med 2006 20: 25
DOI: 10.1191/0269216306pm1125oa

Palliative Medicine 2006; **20:** s25–s30

Transdermal buprenorphine in cancer pain and palliative care

Reinhard Sittl Department of Anesthesiology, Pain Therapy, University of Erlangen-Nuremberg, Erlangen

Transdermal buprenorphine has been assessed as a therapy for chronic cancer and non-cancer pain in both clinical and postmarketing surveillance studies. Data from 239 patients who had participated in a follow-up study of up to six years have shown efficacy and safety, and good tolerability over prolonged treatment periods with a marked stability of doses. From the cancer pain population (134 patients), 20% stayed on transdermal buprenorphine until the end of their lives. Postmarketing surveillance study data from 13 179 patients, including 3690 cancer patients assessed during a 10-week observation period, showed that 81% of patients achieved good/very good pain relief with transdermal buprenorphine. Furthermore, 49.6% of patients did not require any analgesic comedication or rescue therapy, a point that is particularly important in the elderly population. Results from the Spanish Pain Society on transdermal buprenorphine in chronic non-cancer, neuropathic and cancer-related pain, and on switching from morphine, also confirmed its beneficial efficacy and safety, and showed that buprenorphine does not antagonize pain relief, or cause withdrawal when combined with full μ-agonists. The effectiveness of buprenorphine is further supported by evidence of its pronounced anti-hyperalgesic effect in a human pain model, which may be a factor in explaining the efficacy of buprenorphine in neuropathic pain. When switching of opioids is indicated to improve pain relief or reduce adverse events, equipotency dosage ratios are important. The equipotency ratio for morphine to buprenorphine, previously established as 75:1, is now being questioned as new data from a retrospective cohort study were published indicating a ratio of 100:1. Moreover, transdermal buprenorphine has superior safety in respect to respiratory depression, immunological and renal effects compared with standard World Health Organization step III opioids, which makes it highly suitable for treating moderate-to-severe pain also in cancer patients, a *per se* vulnerable patient population requiring a sensible selection of potent analgesics. *Palliative Medicine* 2006; **20:** s25–s30

Key words: analgesia; antihyperalgesia; buprenorphine; cancer pain; neuropathic pain; opioid; palliative care; switching; transdermal

Introduction

Adult and child patients, and their friends and relatives, frequently assert that adequate pain management is the key determining factor in successful palliative care. It is a precondition for psychological support and for the frank and open communication that is vital for symptom control. Individual nursing, pastoral and spiritual care are also made easier in the last days of life when satisfactory pain relief can be achieved.

Buprenorphine and cancer pain

Opioids play a major role in the treatment of cancer pain, and morphine remains the gold standard for analgesia. However, in many countries other strong opioids are also prescribed including hydromorphone, oxycodone, fentanyl and buprenorphine. The partial μ-receptor agonist buprenorphine has been available in a sublingual formulation for many years and also in a transdermal formulation for some time. Although not a new substance, its broad use in analgesia in the past has been restricted due to the association of the substance with various myths and misunderstandings. For example, for many physicians buprenorphine was associated with a ceiling effect in analgesia that could not be countered by an antagonist. This has now been proven to be not the case (see also previous article).

Especially since the new transdermal formulation has been available, buprenorphine has been successfully used in cancer that is associated with severe pain.

A large postmarketing surveillance study of transdermal buprenorphine carried out in Germany in 2001/2002 showed very clearly that doctors do use this modality for

Address for correspondence: Reinhard Sittl, Department of Anaesthesiology, Pain Therapy, University of Erlangen-Nuremberg, Krankenhausstr. 12, D-91054 Erlangen, Germany.
E-mail: Reinhard.Sittl@kfa.imed.uni-erlangen.de

10.1191/0269216306pm1125oa

the treatment of cancer pain.[1] In that study 3690 cancer patients (28% of the total study population) were prescribed the buprenorphine patch, which provided good, sustained and dose-dependent analgesia irrespective of the patient's age. Interestingly, the patients treated with transdermal buprenorphine were most frequently elderly; 44% of the patients were 70 years old or more.[1] This reflects the real-life situation in which most chronic pain patients are elderly, ie, >65 years of age. Also, a total of 134 cancer patients in three randomized, double-blind, placebo-controlled clinical trials of transdermal buprenorphine extended their treatment for up to six years, in an open-label continuation study that demonstrated long-term efficacy and safety.[2–4] The pain scores of these patients on a verbal rating scale were documented, and 86.6% rated their pain relief in this long-term study as complete, good or satisfactory (see Figure 1).

Under the auspices of the Spanish Pain Society, Muriel and colleagues studied the efficacy of transdermal buprenorphine in 164 patients (57% male, 43% female) suffering from various types of cancer, including colon, lung, breast and laryngeal cancer.[6] The study duration was 8 weeks. Subjects had previously been treated with non-opioids, weak opioids and coanalgesics, but in each case the chronic pain score on a visual analogue scale (VAS) remained above 5.

As Figure 2 shows, the initial dose for more than 80% of the subjects was one 35 µg/h patch. However, 15% started treatment with half a 35 µg/h patch; this approach is often adopted in patients who are aged over 70 years, or who weigh less than 50 kg, to avoid an overdose or to prevent side effects. The dosage was titrated against pain and stable dosages were achieved after four weeks, at the levels shown in Figure 2, when a significant reduction in pain intensity had been achieved; the mean VAS pain score had decreased from >7 to <4. No response to

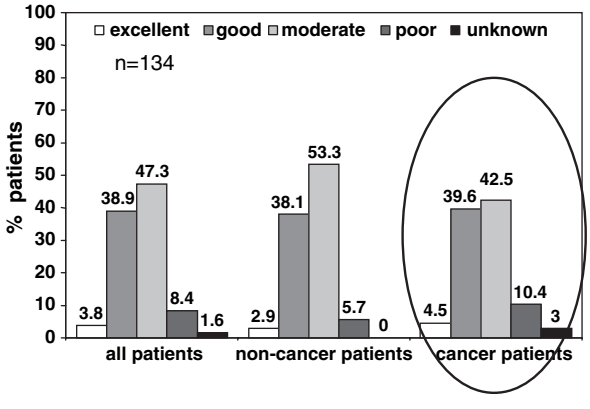

Figure 1 Retrograde assessment of pain relief in the long-term study on transdermal buprenorphine showing a high percentage of cancer patients with good to satisfactory pain relief.[5]

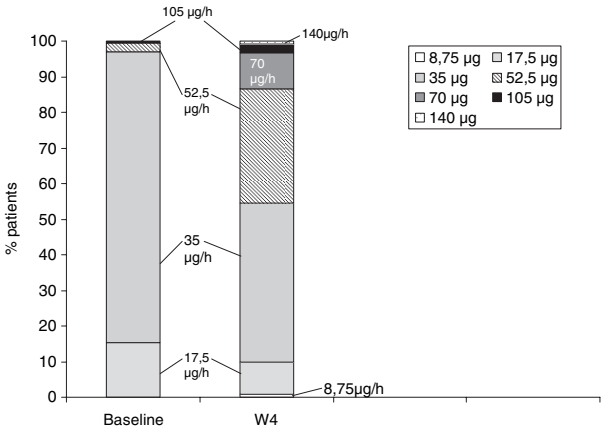

Figure 2 Titration of the dose of transdermal buprenorphine in patients with cancer pain.[6]

buprenorphine treatment was observed in 13.3% of the patients, who were withdrawn from the study.

Regarding safety and tolerability, adverse events were rather high at the beginning of the study, but were well controlled by adjuvant drugs. Over the 8-week observation period the overall incidence of adverse events gradually decreased to a level similar to that found with other opioids. Systemic adverse events affected 45.7% of patients in week 2 and declined to 18% in week 8. As Table 1 shows, most often nausea, vomiting and sedation/somnolence were reported, while the incidence of constipation was less than 10% over the complete study period.

Local adverse events at patch site were mostly mild to moderate in intensity and also tended to subside with time. Most often, erythema with an incidence of 7.3% in week 2 and 4.7% in week 8, and pruritus (4.3% in week 2, 0.8% in week 8) were reported.

While the incidences of nausea and vomiting as the most often reported adverse events are comparable to the adverse event rates of other strong opioids, especially at begin of opioid therapy, the constipation rate in this study stayed at a comparably low rate, from 6.7% in week 2 to 5.5% in week 8. This is in contrast to studies on other opioids such as transdermal fentanyl[7,8] or morphine,[9] where constipation is the most frequently seen persistent side effect. For instance, in their open-label prospective long-term trial in cancer patients who were switched from either codeine or morphine to transdermal fentanyl, Mystakidou and co-workers saw constipation rates between 9 and 20%.[7] Nugent *et al.* reported constipation rates of 28% in non-cancer patients in altogether 87 treatment-months.[8] By contrast, in a large postmarketing surveillance study with transdermal buprenorphine in 13 179 patients, a constipation rate of 0.97% was reported,[1] and another study on the long-term

Table 1 Systemic adverse events reported from week 2 until week 8 in cancer pain patients of the described study[6]

Timepoint (patient number)	Week 2 ($n=158$)		Week 4 ($n=131$)		Week 8 ($n=114$)	
Number and % of adverse events	*n*	%	*n*	%	*n*	%
Nausea	37	22.6	20	13.5	11	8.6
Vomiting	28	17.1	19	12.8	3	2.3
Somnolence/sedation	15	9.1	3	2.0	3	2.3
Constipation	11	6.7	8	5.4	7	5.5
Dizziness	8	4.9	5	3.4	3	2.3
Dry mouth	8	4.9	3	2.0	–	–
Pruritus, systemic	4	2.4	3	2.0	2	1.6
Sweating	4	2.4	1	0.7	1	0.8
Others	9	5.4	7	4.8	3	2.4

performance of transdermal buprenorphine in chronic pain reported constipation rates of 3.8%.[5]

Thus it can be concluded that transdermal buprenorphine is an efficient and safe opioid analgesic for the treatment of cancer pain. It is effective in most patients and the incidence and nature of side effects are similar to those of other opioids, except for a lesser rate of constipation.

Buprenorphine and neuropathic pain

Cancer pain often has a neuropathic component. In recent months a number of animal studies, case reports and clinical trials have been published that indicate that buprenorphine may offer some advantages in the treatment of neuropathic pain. In preclinical animal studies, Christoph and colleagues showed that buprenorphine was fully effective in the nerve ligation model in rodents, providing analgesia in various pain conditions that included neuropathic pain.[10] Buprenorphine also strongly inhibited mechanical and cold allodynia in mononeuropathic rats, and mechanical hyperalgesia and cold allodynia in polyneuropathic rats. In a published collection of clinical case studies of complicated pain syndromes, which included neuropathic and mixed pain syndromes, patients benefited by rotating to buprenorphine from other analgesics.[11] In each case, buprenorphine provided satisfactory pain relief and no problems were encountered on switching from previous analgesics, including high doses of other opioids.

The effectiveness of transdermal buprenorphine in neuropathic pain has also been investigated by Rodriguez *et al.*, again on behalf of the Spanish Pain Society.[12] The study population of 237 patients (37% male, 63% female) suffered from various typical neuropathic symptoms, and pain syndromes in which neuropathic pain constituted a major component (see Table 2). The study duration was 4 weeks. Prior treatment included anti-convulsants (75.5%), anti-depressants (64.6%) and non-opioid analgesics (50.6%). Any concomitant treatment was not changed during the study.

The proportion of patients that started treatment with one 35 μg/h patch was 70.5%, while 29.1% began with half a 35 μg/h patch. Again, the dose was titrated to the pain and after 4 weeks a stable dosage was achieved, accompanied by a significant reduction in the total pain score. Figure 3 shows the efficacy of transdermal buprenorphine with respect to the different characteristics of neuropathic pain, assessed using the McGill Pain Scale. There is a clear decrease in the percentage of patients reporting moderate to severe pain and a corresponding increase in the percentage reporting none or only slight pain. The drop-out rate was 32%, which is similar to other studies in which strong opioids have been used to treat neuropathic pain.

It has been suggested that one property that might contribute to the efficacy of buprenorphine in neuropathic pain is its pronounced anti-hyperalgesic effect. The analgesic and anti-hyperalgesic properties of sublingual and intravenous buprenorphine and their relationship with other opioids have been investigated by Koppert and colleagues, using the electric pain model.[13] In this model two stainless steel wires are inserted intradermally into the forearm of volunteers and connected to a current generator. In the Koppert study, the current was gradually increased until an NRS pain score

Table 2 Numbers and percentages of patients with listed diagnoses in the neuropathic pain study

	Number (*n*)	%
Lumbar and sciatic pain	59	29.9
Failed back surgery pain syndrome	30	12.7
Cervical/cervicobrachial pain	32	13.5
Postherpetic neuralgia	29	12.2
Trigeminal neuralgia	13	5.5
Complex regional pain syndrome (types I/II)	12	5.1
Diabetic neuropathy	12	5.1
Postoperative neuropathic pain	8	3.4
Others	42	17.8

Modified from: Rodriguez *et al.*, 2004.[12]

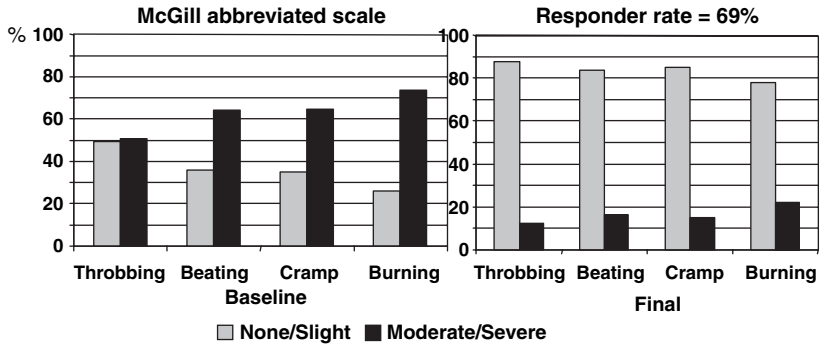

Figure 3 Change of pain qualities during therapy with transdermal buprenorphine in neuropathic pain
Modified from: Rodriguez *et al.*[12]

of 6 was reached, when the volunteers developed a stable area of hyperalgesia around the insertion of the wires. This study found that buprenorphine could reduce the area of hyperalgesia more than fentanyl and alfentanil, and almost as much as S-ketamine.[13] The mechanism for this pronounced anti-hyperalgesic effect is not well understood, but may be associated with the fact that buprenorphine's receptor subtype selectivity, binding characteristics and coupling to opioid receptor G-protein are quite different from those of typical μ-agonists.

Koppert *et al*. also confirmed in their study that obviously different mechanisms are responsible for opioid-induced analgesia and anti-hyperalgesia.[13] In fact, it had been formerly shown that apart from their analgesic effect, pure μ-opioid agonists such as fentanyl produce hyperalgesia,[14–16] while buprenorphine rather exerted a long-lasting *anti*-hyperalgesic effect. In his editorial recently published in *Pain*,[17] Simonnet in fact proposed to distinguish between two different classes of opioids independently of their analgesic potencies according to their anti-hyperalgesic effect.

The phenomenon of anti-hyperalgesia probably has an impact on all pain states dominated by central sensitization, among them neuropathic pain. This is why buprenorphine is one of most promising agents in neuropathic pain.

No antagonistic effects between buprenorphine and fentanyl

In another as yet unpublished double-blind, crossover, placebo-controlled study in human volunteers, the analgesic and anti-hyperalgesic effects of buprenorphine and fentanyl were assessed using the same electric pain model.[18] After electrically evoking pain, the administration of placebo was followed by only a small reduction in pain score measured on a numeric rating scale (NRS) (Figure 4). By contrast, a dose of 1.5 μg/kg of fentanyl (about 0.1 mg in a 70 kg man) produced a rapid and considerable decrease in pain score, and an identical dose of buprenorphine had a very similar effect, although the onset of analgesia took slightly longer. Combining a half dose of both drugs (0.75 μg/kg of each) resulted in a very similar decrease in pain score to a full dose of either opioid, and there were no antagonistic effects between the two opioids seen in this model. In fact, both drugs

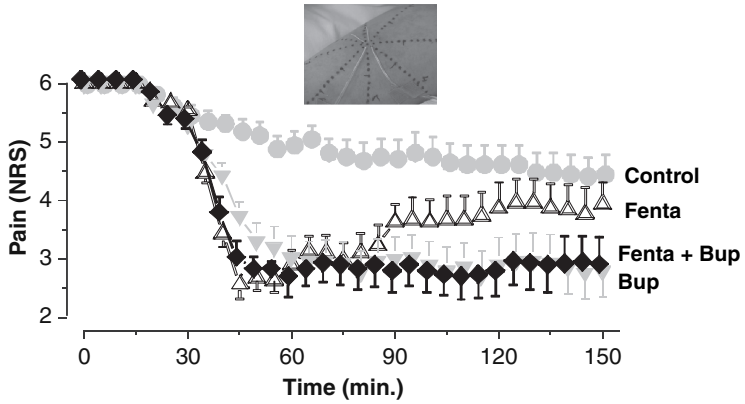

Figure 4 Time-course of electrically evoked pain ratings (NRS scale) after single administration of fentanyl or buprenorphine (1.5 μg/kg) and their combination (0.75 μg/kg each) in volunteers (electric pain model).[18]

Table 3 Equipotent doses of some common opioids

Alternative opioid	Equipotent dose of oral morphine
Transdermal fentanyl	×100
Oxycodone	×2
Hydromorphone	×7.5
Transdermal buprenorphine	×100

seemed rather to reinforce each other in their analgesic and anti-hyperalgesic effects, indicating that buprenorphine can be combined with full μ-opioid agonists such as fentanyl, at least in the model used in this study.

Equivalence and breakthrough pain

Opioid switching is one method of improving pain relief or reducing the incidence of side effects that is often used in cancer patients. It is recommended that conversion tables are used to obtain the equipotent dosage of an alternative opioid. The conversion table shown in Table 3 is used at the University Hospital in Erlangen.

According to older literature, the ratio of morphine to transdermal buprenorphine was around 70:1. However, newer results from a retrospective cohort study suggest it might be higher at 100:1.[19] Clinical data from an open-label study on patients who were switched from high-dose morphine to transdermal buprenorphine seem to confirm this (Grünenthal, data on file, publication in preparation; Figure 5). On the left-hand side of the figure it can be seen that more than 80% of the patients who had previously been treated with 120 mg/day of morphine achieved satisfactory pain relief by simply switching to the 52.5 μg/h buprenorphine patch. This patch provides 1.2 mg of buprenorphine per day, giving an equivalence ratio of 100:1. In patients who were receiving higher doses of morphine, individual titration was necessary to establish the correct dose of transdermal buprenorphine. In patients on extremely high doses (500–1000 mg/day) a patient-controlled analgesia (PCA) pump is recommended for this purpose.

Breakthrough pain

When treating patients with long-acting opioid formulations, breakthrough pain is best treated with a rapid-onset, short-acting opioid, especially in the initial titration phase of therapy. The World Health Organization (WHO) recommends using the same opioid, so for a patient receiving transdermal buprenorphine, the first choice would be sublingual buprenorphine. However, it is also possible to combine buprenorphine with other μ-agonists, so a second choice would be immediate-release morphine or transmucosal fentanyl. In patients whose dose of transdermal buprenorphine is relatively small (35 μg/h or less), tramadol drops would be a third option.

Conclusions

Transdermal buprenorphine can be used successfully in the management of cancer pain, for which it provides effective pain relief, and no ceiling effect has been observed within the therapeutic dose range with respect to analgesia. Some data indicate that buprenorphine is particularly suitable for treating neuropathic pain.

Further studies are required to determine the drug of first choice in individual patients and in special pain syndromes. Pharmacogenetic studies will soon provide more information on which to base treatment decisions. However, successful cancer pain management is already possible today, and transdermal buprenorphine is one valuable option for achieving that goal.

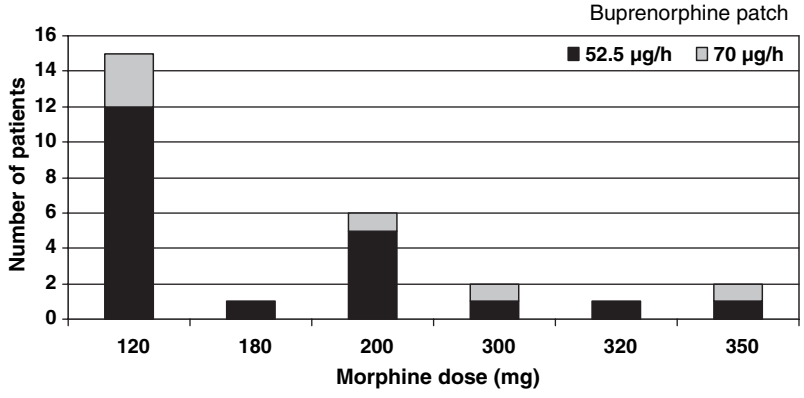

Figure 5 Switching from high-dose morphine to transdermal buprenorphine in an open-label study.

References

1 Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice – a post-marketing surveillance study in 13179 patients. *Curr Med Res Opin* 2005; **21**: 1147–56.

2 Böhme K, Likar R. Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain: a randomised, double-blind, placebo-controlled study. *Pain Clinic* 2003; **15**: 193–202.

3 Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2004; **26**: 1808–19.

4 Sittl R, Griessinger N and Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2003; **25**: 150–68.

5 Likar R, Kayser H, Sittl R. Transdermal buprenorphine for long-term management of chronic cancer and noncancer pain. Results of an open-label, multicentre, follow-up study. *Book of Abstracts*, International Forum on Pain Medicine. Sofia, 2005.

6 Muriel C, and the Opioid Study Group of the Spanish Pain Society. Assessment of the transdermal buprenorphine patch in patients with cancer pain. *Rev Soc Esp Dolor* 2004; **11**: 41–48.

7 Mystakidou K, Parpa E, Tsilika E, *et al*. Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. *J Pain* 2003; **4**: 298–306.

8 Nugent M, Davis C, Brooks D, *et al*. Long-term observations of patients receiving transdermal fentanyl after a randomized trial. *J Pain Symptom Manage* 2001; **21**: 385–91.

9 Hanks GW, De Conno F, Cherny N, *et al.*; Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; **84**: 587–93.

10 Christoph T, Kögel B, Schiene K *et al.* Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. *Eur J Pharmacol* 2005; **507**: 87–98.

11 Likar R, Sittl R. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. *Anesth Analg* 2005; **100**: 781–85.

12 Rodriguez MJ and the Opioid Study Group of the Spanish Pain Society. Transdermal buprenorphine in neuropathic pain. *Rev Soc Esp Dolor* 2004; Suppl 5: 11–21.

13 Koppert W, Ihmsen H, Körber N, *et al*. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* 2005; **118**: 15–22.

14 Angst MS, Koppert W, Pahl I, *et al*. Short-term infusion of the μ-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain* 2003; **106**: 49–57.

15 Celerier E, Laulin JP, Larcher A, *et al*. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology* 2000; **92**: 465–72.

16 Guignard F, Chauvin M, Miller JC, *et al*. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000; **93**: 409–17.

17 Simonnet G. Opioids: from analgesia to anti-hyperalgesia? Editorial. *Pain* 2005; **118**: 1–2.

18 Tröster A, Sittl R, Singler B, *et al*. Quantification of analgesic and antihyperalgesic effects of buprenorphine and fentanyl in healthy volunteers. *Book of Abstracts*, 3rd World Congress of the World Institute Of Pain, Barcelona, 2004: 74.

19 Sittl R, Likar R, Poulsen Nautrup B. Equipotent doses of transdermal fentanyl and buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. *Clin Ther* 2005; **27**: 225–37.