Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

Augusto Caraceni, Geoffrey Hanks*, Stein Kaasa*, Michael I Bennett, Cinzia Brunelli, Nathan Cherny, Ola Dale, Franco De Conno, Marie Fallon, Magdi Hanna, Dagny Faksvåg Haugen, Gitte Juhl, Samuel King, Pål Klepstad, Eivor A Laugsand, Marco Maltoni, Sebastiano Mercadante, Maria Nabal, Alessandra Pigni, Lukas Radbruch, Colette Reid, Per Sjogren, Patrick C Stone, Davide Tassinari, Giovambattista Zeppetella, for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC)*

Here we provide the updated version of the guidelines of the European Association for Palliative Care (EAPC) on the use of opioids for the treatment of cancer pain. The update was undertaken by the European Palliative Care Research Collaborative. Previous EAPC guidelines were reviewed and compared with other currently available guidelines, and consensus recommendations were created by formal international expert panel. The content of the guidelines was defined according to several topics, each of which was assigned to collaborators who developed systematic literature reviews with a common methodology. The recommendations were developed by a writing committee that combined the evidence derived from the systematic reviews with the panellists' evaluations in a co-authored process, and were endorsed by the EAPC Board of Directors. The guidelines are presented as a list of 16 evidence-based recommendations developed according to the Grading of Recommendations Assessment, Development and Evaluation system.

Lancet Oncol 2012; 13: e58–68

*These authors contributed equally

Palliative Care, Pain Therapy and Rehabilitation, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (Prof A Caraceni MD, C Brunelli ScD, A Pigni MD); **Department of Palliative Medicine, Bristol Haematology & Oncology Centre, University of Bristol, Bristol, UK** (Prof G Hanks DSc (Med), S King MRCP, C Reid MD); **Department of Cancer Research and Molecular Medicine, Faculty of Medicine** (Prof A Caraceni, Prof S Kaasa MD, E A Laugsand MD), **and European Palliative Care Research Centre (PRC), Department of Circulation and Medical Imaging** (Prof O Dale MD, P Klepstad MD) **and Department of Cancer Research and Molecular Medicine** (D F Haugen PhD), **Norwegian University of Science and Technology (NTNU), Trondheim, Norway; Department of Oncology** (Prof S Kaasa), **and Department of Anesthesiology and Emergency Medicine** (P Klepstad), **St Olav University Hospital, Trondheim, Norway; Leeds Institute of Health Sciences, University of Leeds, Leeds, UK** (Prof M I Bennett MD); **Department of Oncology, Shaare Zedek Medical Centre, Jerusalem, Israel** (Prof N Cherny MD); **European Association of Palliative Care, Milan, Italy** (F De Conno MD); **St Columbia's Hospice, University of Edinburgh, Edinburgh, UK** (Prof M Fallon MD); **Analgesics and Pain Research Unit, King's College London, London, UK** (M Hanna FCA); **Regional Centre of Excellence for Palliative Care, Western Norway, Haukeland University Hospital, Bergen, Norway** (D F Haugen); **Palliative Care Unit, Department of**

Introduction

Moderate to severe pain in cancer is common and affects 70–80% of patients with advanced disease. We have the means and the knowledge to relieve most pain in cancer for most patients,[1] but evidence from surveys and observational studies shows that many patients have troublesome or severe pain and do not get adequate relief.[2]

The skilled use of opioid analgesics is crucial to the relief of cancer pain, but there is a shocking lack of evidence to support clinical practice. The so-called analgesic ladder is the central idea of the WHO 1996 guidelines on cancer pain relief,[3] in which the choice of analgesic is determined by the severity of the pain. The WHO method has been adopted worldwide but the lack of up-to-date evidence, knowledge, and opioid availability have obstructed the path to effective relief of cancer pain.[2,4]

Randomised controlled trials (RCTs) in patients with cancer pain are beset by difficulties.[5] In the absence of hard evidence from RCTs, expert consensus and clinical guidelines might be helpful, because cancer pain relief is a specialist area but most care is delivered by non-specialist practitioners. The European Association for Palliative Care (EAPC) research network published its first guidelines on the use of morphine and alternative opioids in cancer pain in 1996,[6] and published an update in 2001.[7] In this Review we present further work done to strengthen the scope of the EAPC recommendations by the application of rigorous, evidence-based methodology.

Development of recommendations

A comprehensive list of relevant topics on opioid use for cancer pain was derived from a comparison of the previous EAPC recommendations with other available guidelines on cancer pain relief. This list was submitted to a formalised expert consensus process that led to 30 practical clinical questions being summarised in 22 topics.[8,9] The subsequent guidelines development process followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[10–13]

Each of the 22 topics was assigned to a group of collaborators who did a systematic review according to a standardised method (appendix). The results were presented at the Fifth Bristol Opioids Conference, Bristol, UK, Feb 8–9, 2010. 19 reviews have since been published.[14–32] Within each topic the evidence profile for each relevant outcome was determined and this formed the basis for a final recommendation.

In the review of opioids in liver failure[31] and on the use of opioid combinations,[32] evidence did not reach sufficient quality to support a recommendation and, therefore, these areas were not included in this guideline. Our literature review on the treatment of opioid-related constipation completely overlapped with a Cochrane review[33] and it was not submitted for publication. Finally one topic on the role of ketamine was not included because of the lack of resources to complete the work. Thus, 16 recommendations have been included in this summary paper by the writing committee, on the basis of the evidence profiles, modified to take into account individual judgments and evaluations. They have been circulated to the Scientific Advisory Board of the European Palliative Care Research Collaborative, the Board of Directors of the EAPC and to each collaborator for comment and modification as necessary. With this feedback the recommendations were revised by the writing committee and circulated to the whole group once more for comment and final approval.

In this paper and associated publications we have adopted the terms step II opioids and step III opioids to differentiate between low-potency drugs, such as codeine and tramadol, and higher-potency drugs, of which morphine is the prototype. This terminology relates directly to the WHO cancer pain relief ladder and is widely understood.

Anaesthesia, Copenhagen University Hospital Herlev, Herlev, Denmark (G Juhl MD); **Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy** (M Maltoni MD); **Anaesthesia and Intensive Care Unit, Pain Relief and Palliative Care Unit, La Maddalena Cancer Centre, Palermo** (S Mercadante MD); **Department of Anaesthesia and Intensive Care, Palliative Medicine, University of Palermo, Palermo, Italy** (S Mercadante); **Palliative Care Supportive Team, Hospital Universitario Arnau de Vilanova, Lleida, Spain** (M Nabal MD); **Department of Palliative Medicine, University Hospital Bonn, Bonn, Germany** (Prof L Radbruch MD); **Multidisciplinary Pain Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark** (Prof P Sjogren MD); **Population Health Sciences and Education, St George's University of London, London, UK** (P C Stone MD); **Supportive and Palliative Care Unit, Department of Oncology, City Hospital, Rimini, Italy** (D Tassinari MD); **and Patient Services, St Clare Hospice, Hastingwood, UK** (G Zeppetella FRCP)

Correspondence to: Prof Augusto Caraceni, Palliative Care, Pain Therapy, and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, 20133 Milan, Italy
augusto.caraceni@istitutotumori.mi.it

For more on **GRADE** see http://www.gradeworkinggroup.org/

See Online for appendix

Cost-benefit analysis is considered in the GRADE system but there is also an option to omit this feature.[10–13] We decided not to include pharmacoeconomic considerations because of their poor general value and their specific need to be locally adapted and adopted.

EAPC recommendations

WHO step II opioids

Findings

Step II opioids (table 1) have been traditionally used for moderate cancer pain. The systematic review showed that codeine and tramadol are effective compared with placebo.[15] The analgesic effect of paracetamol in conjunction with codeine was shown in an RCT[34] that compared 150 mg codeine alone with 60 mg codeine plus 600 mg paracetamol, and showed that the combination four times per day was as effective and safe as codeine alone twice daily.

Only one RCT provided direct comparative data for the step II opioids, and it showed no difference in efficacy between tramadol, codeine plus paracetamol, and hydrocodone plus paracetamol, although tramadol was associated with more side-effects.[35] Tramadol was compared with morphine in a separate RCT,[36] which predictably showed better efficacy but also more side-effects with morphine. The utility of step II opioids in the WHO method has been addressed in three trials,[37–39] all of which have significant methodological flaws, insufficient statistical power, and selection bias. Overall, the limited evidence provided by these studies shows that oral morphine at low doses can be used in opioid-naive cancer patients and that in some patients pain relief might be better than that achieved with step II drugs. No evidence showed that initiating opioid therapy by using a step II drug improves overall management of cancer pain, but the same was found for step III drugs (table 1).

Recommendation for WHO step II opioids

For patients with mild to moderate pain or whose pain is not adequately controlled by paracetamol or a non-steroidal anti-inflammatory drug (NSAID) given regularly by mouth, the addition of a step II opioid (eg, codeine or tramadol; table 1) given orally might achieve good pain relief without troublesome adverse effects. Alternatively, low doses of a step III opioid (eg, morphine or oxycodone; table 1) may be used instead of codeine or tramadol. The data permit a weak recommendation to start a step II opioid in these circumstances.

	Characteristics and comments
Codeine	Step II drug only: use alone or in combination with paracetamol; daily doses ≥360 mg not recommended
Tramadol	Step II drug only: use alone or in combination with paracetamol; daily doses ≥400 mg not recommended
Hydrocodone	Step II drug only: used as a substitute for codeine in some countries
Oxycodone	Step II opioid when used at low doses (eg, ≤20 mg per day) alone or in combination with paracetamol
Morphine	Step II opioid when used at low doses (eg, ≤30 mg per day)
Hydromorphone	Step II opioid when used at low doses (eg, ≤4 mg per day)

*Originally classified as weak opioids.

Table 1: **WHO step II opioids* for moderate cancer pain in opioid-naive patients**

WHO step III opioid of first choice

Findings

Morphine is the prototype opioid analgesic, and for 25 years oral morphine has been deemed the drug of first choice for treating moderate to severe cancer pain. Morphine has remained the first choice for reasons of familiarity, availability, and cost rather than proven superiority.

Many novel formulations of old opioids, such as oxycodone, hydromorphone, and fentanyl, have been developed and the availability of different opioids across the world has improved.

Two systematic reviews support the use of oral morphine for cancer pain,[14,40] one systematic review of oxycodone updates an earlier review and meta-analysis,[19] and one review supports the use of hydromorphone.[20] These reviews included nine randomised trials that compared oral administration of morphine, oxycodone, and hydromorphone and involved 654 patients. Eight were designed as superiority trials and seven of these showed no significant differences in efficacy. Similar results were reported in the only meta-analysis of oxycodone compared with morphine or hydromorphone in four studies.[41] One unpublished trial showed a difference with slight significance in favour of morphine compared with hydromorphone.[40] One trial demonstrated equivalence for morphine and hydromorphone.[42] The comparison of the tolerability profiles of the three opioids was similar.[14,40]

The indirectness of the studies should be taken into consideration for this recommendation, but a high level of consistency was seen for efficacy and toxic effects.

Recommendation for WHO step III opioid of first choice

The data show no important differences between morphine, oxycodone, and hydromorphone given by the oral route and permit a weak recommendation that any one of these three drugs can be used as the first choice step III opioid for moderate to severe cancer pain.

Opioid titration

Findings

The long-standing practice of using immediate-release oral morphine every 4 h to start morphine administration is not based on controlled clinical trials, but on the pharmacokinetic profile of this formulation (t_{max} <1 h; $t_{1/2\beta}$ 2–3 h; duration of effect about 4 h).[43,44] Individualisation of the dose of opioid is achieved by starting at a low dose and titrating upwards until the desired effect is achieved.[45] With the introduction of oral and transdermal slow-release

opioids, clinicians were encouraged initially to titrate an immediate-release opioid and switch to a modified-release preparation.[7] Immediate-release formulations are much more flexible than long-acting preparations, both in the dose titration period and when the pain is poorly controlled.

As confidence has grown with long-acting formulations, many practitioners have explored their use when starting treatment with oral opioids in patients at home, and have found this approach to work well.

A systematic literature review[16] identified only two clinical trials that specifically addressed the different approaches to dose titration when starting oral morphine. One RCT included 40 patients and showed no significant differences between immediate-release and modified-release oral morphine titration.[46] The other study was an open-label trial in 62 patients, and showed that intravenous morphine titration allowed faster achievement of pain control than did use of oral morphine, and that both treatments were well tolerated.[47]

Recommendation for opioid titration

The data permit a weak recommendation that immediate-release and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration. The titration schedules for both types of formulation should be supplemented with oral immediate-release opioids given as needed.

The role of transdermal opioids

Findings

Transdermal fentanyl and buprenorphine delivery systems enable slow increase of drug plasma levels with very long apparent half-lives (several days) and a long latent period before pharmacological steady states are reached.[48] The uses of these preparations as first-choice step III opioid or as alternatives to step II opioids have been debated. Titration must be done according to the apparent drug half-life—ie, every 3 days with use of immediate-release opioids in the interim.

A systematic review of transdermal fentanyl and buprenorphine for moderate to severe cancer pain[21] includes the results of one meta-analysis of four RCTs that compared oral morphine with fentanyl or buprenorphine[49] and one RCT with three parallel arms that compared oral morphine with fentanyl and methadone.[50] No significant differences in efficacy emerged between either transdermal preparation and other opioids, but a difference in favour of transdermal preparations was seen for constipation, and patients' preference,[49] which suggests that in some cases transdermal opioids are appropriate and effective in patients who have not previously received step III opioids.[50]

None of these trials was blinded, some were of low methodological quality, and two were done in patients already taking step III opioids. Thus, the evidence on this topic is low level and partly indirect.

Among several trials that compared transdermal buprenorphine and placebo, only one was a double-blind RCT. It involved 189 cancer patients and showed a significant difference in the percentages of response between buprenorphine and placebo, in favour of buprenorphine.[51]

Recommendation for the use of transdermal opioids

Transdermal fentanyl and buprenorphine are alternatives to oral opioids. The data permit a weak recommendation that either drug may be the preferred step III opioid for some patients. For patients unable to swallow they are an effective, non-invasive means of opioid delivery.

The role of methadone

Findings

Methadone has often been viewed as an alternative to oral morphine but its specific pharmacokinetic characteristics and a very long and unpredictable half-life[43] require careful individualisation of dosing schedules. Oral methadone is the drug most frequently considered as an option in the practice of opioid switching. In a systematic review by the Cochrane Collaboration,[52] which was updated by Cherny,[22] only three RCTs[50,53,54] involving 277 patients addressed the comparison of methadone with another step III opioid (one study had a third group receiving transdermal fentanyl). The drugs did not differ in efficacy between patients who were treated with step II opioids or were opioid naive. In one study methadone was associated with a higher incidence of sedation, which led to a high percentage of patients dropping out because of adverse effects.[53] In a previous study, four (15%) of 26 versus two (8%) of 26 patients in the methadone and diamorphine plus cocaine groups, respectively, withdrew because of sedation.[55]

Although methodological limitations were found in these three studies, data consistently show no significant differences in analgesic efficacy between methadone and morphine; the evidence of more frequent CNS side-effects (sedation) with methadone is not consistent across studies. Methadone should be considered an alternative to other oral step III opioids.

Recommendation for use of methadone

Methadone has a complex pharmacokinetic profile with an unpredictably long half-life. The data permit a weak recommendation that it can be used as a step III opioid of first or later choice for moderate to severe cancer pain. It should be used only by experienced professionals.

Opioid switching

Findings

Opioid switching is the term given to the clinical practice of substituting one step III opioid with another when a satisfactory balance between pain relief and adverse effects is not achieved with appropriate titration of the first opioid. This practice might be explained

pharmacologically by the phenomenon of incomplete cross tolerance.[56,57] A Cochrane review[58] and an updated systematic review[23] identified no randomised trial that supports the practice of opioid switching. The available uncontrolled trials involved 679 patients[23,58] and showed that opioid switching is done more often when pain is not well controlled and side-effects limit dose escalation than when pain is not controlled but the side-effects are tolerable. The apparent success rates of switching ranges from 40% to 80% and the most frequent switch is from morphine, hydromorphone, or fentanyl to methadone.

Recommendation for opioid switching

The data permit a weak recommendation that patients receiving step III opioids who do not achieve adequate analgesia and have side-effects that are severe, unmanageable, or both, might benefit from switching to an alternative opioid.

Relative opioid analgesic potencies

Findings

The practice of switching from one opioid drug to another because of unsatisfactory analgesia requires that the new drug is prescribed in a dose that is safe and efficacious. Equipotency dose calculations in crossover studies and with acute dose administrations in patients with little or no previous exposure to the opioid under study led to the first equianalgesic tables.[57]

Later calculations of practical equianalgesic dose ratios were derived from RCTs that compared the efficacy of two drugs or from observational case series that described opioid switching during chronic administration. The review by Mercadante and Caraceni[24] specifically addressed the evidence derived from six RCTs with crossover designs and from 26 case series. The most robust data come from patients who were stabilised at equianalgesic doses of oxycodone and morphine (four RCTs), oxycodone and hydromorphone (one RCT), and hydromorphone and morphine (one RCT) before being crossed over. The conversion ratios for switching from oral opioids to fentanyl are based on only one case series, although the quality of the data was high.[24] The assessment of 26 case series shows that variability in the reasons for switching (ie, poor analgesia, opioid-related side-effects, or both), preswitching opioid titration, and overall opioid exposure mean the conversion ratios are approximate indications when they are applied to clinical practice. In many cases the use of a suggested ratio resulted in the need for further dose titration, and clinical experience suggests that the second opioid should be started at a dose lower than that calculated from published equipotency ratios.

	Relative analgesic ratio	Strength of the recommendation for use
Oral morphine to oral oxycodone	1:1·5	Strong
Oral oxycodone to oral hydromorphone	1:4	Strong
Oral morphine to oral hydromorphone	1:5	Weak
Oral morphine to TD buprenorphine*	75:1	Weak
Oral morphine to TD fentanyl†	100:1	Strong

TD=transdermal. *Example: 60 mg oral morphine to 35 μg/h TD buprenorphine (equivalent to 0·8 mg per 24 h). †Example: 60 mg oral morphine to 25 μg/h TD fentanyl (equivalent to 0·6 mg per 24 h).

Table 2: **Relative analgesic ratios for opioid switching**

The conversion ratio from oral morphine to oral methadone is affected by previous opioid use and varies widely from 1:5 to 1:12 or more.[24] Calculation is also complicated by the long half-life of the drug. For this reason conversion ratios to methadone are not included in these recommendations.

Recommendation for relative opioid analgesic potencies

When switching from one opioid drug to another, dose conversion ratios can be recommended with different levels of confidence (table 2). These conversion ratios are specific for patients in whom analgesia from the first opioid is satisfactory. Therefore, when the opioid is switched because of unsatisfactory analgesia, excessive side-effects, or both, clinical experience suggests that the starting dose should be lower than that calculated from published equianalgesic ratios. In all cases the dose needs to be titrated in accordance with clinical response.

Alternative systemic routes of opioid administration

Findings

Parenteral opioid administration might be necessary for patients who cannot swallow, those with nausea and vomiting, or those at the end of life who are unable to continue with oral medication because of weakness or debility.[59,60] A systematic literature review found 18 studies comparing different routes of administration for cancer pain control.[29] In addition three systematic reviews were judged to be relevant to the topic.[40,61,62]

Four studies compared subcutaneous and intravenous opioid infusions, but only one was a high-quality, double-blind, double-dummy crossover trial, which included 99 patients. These studies showed similar efficacy and tolerability with both types of administration and no difference in the dose used, but pain relief was faster with the intravenous route. These results were confirmed in four studies in which administration was sequentially switched from intravenous to subcutaneous administration. In one of these studies, patients who had received high drug doses intravenously needed the subcutaneous dose to be increased. The remaining studies reported on more than 1100 patients and were uncontrolled observational studies.

Intravenous administration has been considered for rapid titration in cases of severe unrelieved pain,[63–66] and compared with subcutaneous infusion.[67] In one study intravenous titration with 1·5 mg morphine every 10 min was compared with oral morphine titration (5–10 mg)

every 4 h. Pain control could be achieved within 1 h with intravenous administration in most patients.[47]

The relative potency ratio of oral to intravenous morphine in patients receiving chronic treatment for cancer pain was 2·9, and the ratio is similar for oral to subcutaneous morphine.[68]

Rectal morphine administration was investigated in two RCTs in comparison with oral and subcutaneous administration, and showed similar pain relief and faster onset of effect.[29]

The use of intravenous or subcutaneous opioid infusion with patient-controlled administration has been investigated in few studies,[69] including two non-blind controlled trials[70,71] and several uncontrolled case series.[72–74]

Recommendation for alternative systemic routes of opioid administration

The data permit three strong recommendations: the subcutaneous route is simple and effective for the administration of morphine, diamorphine, and hydromorphone, and it should be the first choice alternative route for patients unable to receive opioids by oral or transdermal routes; intravenous infusion should be considered when subcutaneous administration is contraindicated (eg, because of peripheral oedema, coagulation disorders, poor peripheral circulation, and need for high volumes and doses); and intravenous administration should be used for opioid titration when rapid pain control is needed.

The data permit four weak recommendations: intravenous and subcutaneous infusions can be used to achieve optimum pain control in patients unable to achieve adequate analgesia with oral and transdermal administration; techniques for patient-controlled analgesia can be adopted for subcutaneous and intravenous opioid infusions in patients who are able and willing to be in control of rescue doses; when switching from oral to subcutaneous and intravenous morphine administration, the relative analgesic potency is the same for both routes and is between 3:1 and 2:1; and, although rectal opioids are effective, appropriate formulations are often not readily available and for many patients are not acceptable, and this route of administration should be used only as a second choice.

Opioids for breakthrough pain

Findings

For the purpose of these guidelines it has been decided to limit the characteristics of breakthrough pain to transitory exacerbations of pain that occur on a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy.[75,76] The Cochrane review by Zeppetella and Ribeiro[77] was updated[25] and a further update was undertaken to include articles published up to June, 2010. Nine studies were available as RCTs involving new preparations of transmucosal oral and intranasal fentanyl. In all studies the patient populations had already been exposed to variable doses of systemic opioids at doses equivalent to at least 60 mg oral morphine. These studies proved that the oral transmucosal and intranasal preparations were associated with better breakthrough pain outcomes than was placebo, and that oral transmucosal fentanyl was more effective than immediate-release oral morphine. Unblinded comparisons have shown that intravenous morphine is superior to oral transmucosal fentanyl in the first 15 min but this difference is no longer evident at 30 min after administration,[78] and that intranasal fentanyl provides a faster onset of analgesia than the oral transmucosal preparation. By comparing the different study results, and with some limitations associated with study quality, the time course of analgesia obtainable from different fentanyl preparations could be summarised (table 3).[79–82]

No simple relation could be demonstrated in the RCTs between the effective doses of oral transmucosal, buccal tablet, and intranasal fentanyl and the 24 h dose of opioid, but an association was evident in two open-label studies[78,79] and has been reported in an observational cohort study.[83] Experienced professionals often start treatment with doses higher than the lowest recommended for patients who are already on high doses of opioids.

Most of the studies reported adverse events, including expected opioid-related side-effects such as sedation and dizziness, as potential limitations of titration to an effective dose of transmucosal, buccal tablet, and intranasal fentanyl. The local mucosal tolerability was good, but some cases of local ulcer have been reported and data on long-term use are limited.[84] Intravenous opioid titration and bolus administration have been also used for improving control of breakthrough pain.[29,85]

Recommendation for opioids for breakthrough pain

The data permit a strong recommendation that pain exacerbations resulting from uncontrolled background pain should be treated with additional doses of immediate-release oral opioids, and that an appropriate titration of around-the-clock opioid therapy should always precede the recourse to potent rescue opioid

	Type of study	Drugs compared	Responder rate (%)*		
			10 min	15 min	30 min
Mercadante et al, 2009[79]	Open-label RCT	INF *vs* OTFC	50% (INF) 20% (OTFC)	70% (INF) 40% (OTFC)	90% (INF) 80% (OTFC)
Kress et al, 2009[80]	Double-blind RCT	INF *vs* placebo	58% (INF)	ND	80% (INF)
Portenoy et al, 2006[81]	Double-blind RCT	FBT *vs* placebo	ND	13% (FBT)	48% (FBT)
Slatkin et al, 2007[82]	Double-blind RCT	FBT *vs* placebo	16% (FBT)	30% (FBT)	51% (FBT)

RCT=randomised controlled trial. INF=intranasal fentanyl. OTFC=oral transmucosal fentanyl. ND=not done. FBT=fentanyl buccal tablets. *33% pain reduction from baseline.

Table 3: **Responder rates after different routes of fentanyl administration in trials with homogeneous outcome measures**

analgesics. Breakthrough pain (eg, incident pain) can be effectively managed with oral, immediate-release opioids or with buccal or intranasal fentanyl preparations. In some cases the buccal or intranasal fentanyl preparations are preferable to immediate-release oral opioids because of more-rapid onset of action and shorter duration of effect. Additionally, the data permit a weak recommendation that immediate-release formulations of opioids with short half-lives should be used to treat pre-emptively predictable episodes of breakthrough pain in the 20–30 min preceding the provoking manoeuvre.

Treatment of opioid-related emesis

Findings

Opioid-induced nausea and vomiting are experienced by up to 40% of cancer patients with no previous emesis. Since this adverse effect is an inconsistent consequence of opioid administration, prophylactic antiemetic medication is not generally prescribed.

The systematic review by Laugsand and colleagues[18] identified nine studies in which relief of nausea and vomiting related to opioid use was the primary outcome. Only two RCTs showed efficacy, which was achieved with high doses of metoclopramide.

50 studies of low quality included nausea, vomiting, or both, as secondary outcomes, and suggested that switching from one opioid to another, changing the route of administration, for instance from oral to transdermal or parenteral, or dose reduction are useful.

Recommendation for treatment of opioid-related emesis

The data permit a weak recommendation that some antidopaminergic drugs (eg, haloperidol) and other drugs with antidopaminergic and additional modes of action (eg, metoclopramide) should be used in patients with opioid-induced emesis.

Treatment of opioid-related constipation

Findings

Prophylactic laxative treatment is frequently given to patients on long-term opioid therapy. The Cochrane systematic analysis by Candy and colleagues[33] reviewed seven RCTs that involved 616 patients. Four of the studies compared different kinds of laxatives (co-danthramer [dantron and poloxamer] *vs* senna; lactulose plus senna *vs* magnesium hydroxide plus liquid paraffin; senna *vs* lactulose; and mishrakanesham [an ayurvedic formulation] *vs* senna) but showed no significant differences between them. Three RCTs showed that methylnaltrexone effectively reversed opioid-related constipation, which was confirmed by a meta-analysis.[33] The success rate with this treatment was about 50%, but the administration of methylnaltrexone has been associated with flatulence and dizziness.[86,87] Dose-related abdominal cramping has been reported,[86,88] but, owing to conflicting results between the two main RCTs,[86,87] this effect was not confirmed at meta-analysis.[33]

One RCT not included in the Cochrane review studied oral naloxone to correct opioid-related constipation, but showed no efficacy.[89]

Recommendation for treatment of opioid-related constipation

The data permit a strong recommendation to routinely prescribe laxatives for the management or prophylaxis of opioid-induced constipation. No evidence suggests that one laxative agent should be recommended over others. A combination of drugs with different modes of action is likely to be more effective in resistant constipation than a single agent. Additionally, methylnaltrexone administered by subcutaneous injection should be considered in the treatment of opioid-related constipation when traditional laxatives are not effective.

Treatment of opioid-related CNS symptoms

Findings

Opioid-related CNS side-effects can be separated into symptoms and signs associated with a lowering level of consciousness (sedation, drowsiness), cognitive and psychomotor impairment, and hyperexcitability reactions (hallucinations, myoclonus, and hyperalgesia). One systematic review focused on these specific opioid CNS side-effects and 25 articles were reviewed.[17]

Four different drugs were identified in 11 publications as treatments for opioid-induced sedation (methylphenidate, donepezil, dexamfetamine, and intravenous caffeine). Methylphenidate administration was assessed in three RCTs: two gave positive results and one was negative, but the quality of the negative study was lower than that of the positive studies. Several side-effects were associated with the use of methylphenidate (anxiety, hallucinations, and sweating). The quality of the studies involving dexamfetamine, caffeine, and donepezil was not sufficient to make any recommendation about their use.

The presence of myoclonus as an adverse effect, mostly of systemically administered but also of spinally administered, opioids was documented in several case series. The evidence on control of myoclonus and hallucinations with symptomatic treatments is limited to case reports. Hyperalgesia has been documented rarely and has generally been managed effectively with dose reduction or opioid switching.

Two RCTs compared methylphenidate or caffeine with placebo and showed improvements in cognitive and psychomotor performance in patients taking long-term opioid therapy.

Recommendation for treatment of opioid-related CNS symptoms

The data permit a weak recommendation that methylphenidate can be used to improve opioid-induced sedation but the threshold between desirable and undesirable effects is narrow. The data also permit a weak recommendation that in patients with opioid-related neurotoxic effects (delirium, hallucination, myoclonus,

and hyperalgesia), dose reduction or opioid switching should be considered.

Use of opioids in patients with renal failure

Findings

Particular caution with the use of opioids in cancer patients with impaired renal function has been the object of several guidelines, expert opinions, and interpretations. Recommendations have been based on known opioid pharmacokinetics, which might lead to the accumulation of the parent drug and its metabolites in patients with renal failure.

The systematic literature review by King and colleagues[26] identified 15 studies (eight prospective observational trials and seven retrospective studies) that specifically reported on clinical outcomes relevant to the use of opioids for cancer pain in patients with renal impairment. All these studies, however, were of low quality. More observations are available for morphine than for other opioids but the evidence that morphine metabolites have a role in causing side-effects in patients with renal failure is inconsistent. Guidelines so far, therefore, have been based on general caution criteria and indirect pharmacological evidence.

Recommendation for use of opioids in patients with renal failure

The data permit a weak recommendation that in patients with severe impairments of renal function (glomerular filtration rate <30 mL/min) opioids should be used with caution. The opioid of first choice should be fentanyl or buprenorphine administered subcutaneously or intravenously at low starting doses and with subsequent careful titration. Alternative strategies, for instance reductions in dose or frequency of administration of morphine, might be adequate short-term strategies.

Role of paracetamol and NSAIDs in addition to step III opioids

Findings

The first step of the WHO analgesic ladder recommends the use of paracetamol or NSAIDs without opioids; combination with opioids is possible as part of step II and step III. Our recommendation, however, only addresses use of these drugs in combination with step III opioids.

In a Cochrane review updated to March, 2003,[90] 42 eligible trials were identified. The evidence supported the superiority of NSAIDs and paracetamol to placebo, but no difference could be found between different NSAIDs. Concerning the addition of NSAIDs or paracetamol to step III opioids, five placebo-controlled, double-blind RCTs were identified. Another review[32] found seven further articles, giving a total of 12 eligible studies (seven of NSAIDs and five of paracetamol). Three studies showed increased analgesia and two a decrease in opioid consumption with combined NSAIDs and opioids. In one study a mean difference of 0·4 on a 0–10 numerical pain-intensity rating scale was found in favour of paracetamol. One study showed a higher prevalence of gastrointestinal side-effects in patients treated with opioids and NSAIDs than in patients treated with opioids alone. In general, trial design and duration of reviewed studies were not adequate to enable assessment of the side-effects of long-term NSAID use in this population, but caution was recommended, particularly the high-risk elderly population, because of these drugs' known gastrointestinal, renal, and cardiovascular toxic effects.[91]

All these studies had substantial limitations because of the heterogeneity in designs, populations, and outcome measures and the lack of long-term evaluation.

Recommendation for role of paracetamol and NSAIDs in addition to step III opioids

The data permit a weak recommendation to add NSAIDs to step III opioids to improve analgesia or reduce the opioid dose required to achieve analgesia. The use of NSAIDs, however, should be restricted because of the risks of serious adverse effects, in particular in elderly patients and those with renal, hepatic, or cardiac failure. The data also permit a weak recommendation that paracetamol should be preferred to NSAIDs in combination with step III opioids because of a more favourable side-effect profile, but its efficacy is not well documented.

Role of adjuvant drugs for neuropathic pain (antidepressants and anticonvulsants)

Findings

Cancer pain is mediated by a mixture of nociceptive and neuropathic mechanisms. Adjuvant analgesics are often added to opioids to target specific neuropathic pain mechanisms. The most frequently used adjuvant drugs for neuropathic pain are tricyclic antidepressants, such as amitriptyline and imipramine, and antiepileptics, such as gabapentin and pregabalin. A systematic literature review that specifically addressed this topic identified five RCTs.[27] Definitions of neuropathic cancer pain were available in all studies but were inconsistent across them. Only two trials were placebo controlled; one was of gabapentin and the other one of amitriptyline, both as add-on therapy to opioid analgesics. These two studies showed an additional analgesic effect on pain intensity. Pain relief was associated with adverse events, usually CNS side-effects and in particular somnolence and dizziness, with one case of respiratory depression.

Recommendation for the role of adjuvant drugs for neuropathic pain

The data permit a strong recommendation that amitriptyline or gabapentin should be considered for patients with neuropathic cancer pain that is only partially responsive to opioid analgesia. The combination of an opioid with these drugs is likely to cause more CNS

Search strategy and selection criteria

We did a systematic search for English-language randomised and non-randomised trials and meta-analyses that involved human adults with chronic cancer pain and contained data on efficacy, side-effects, or both, of the treatment considered and described relevant outcomes associated with each topic. We electronically searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from the inception of each database to July 31, 2009. The search terms were text words and MeSH/EMTREE terms specifically relevant to each outcome. We also manually searched the references list of identified papers. See appendix for further search details.

adverse events unless careful titration of both drugs is undertaken.

Spinal route of opioid administration

Findings

The spinal route of administration for opioids has been used for many years in the management of cancer pain. The potential reduction of opioid side-effects by use of this type of administration and the opportunity to add specific adjuvant drugs might be beneficial for patients in whom analgesia is insufficient, side-effects due to systemic opioid administration are severe, or both. The use of other agents that did not involve spinal administration of opioids was not considered in this recommendation.

The literature search done by Kurita and colleagues[28] identified 42 relevant articles published between 1982 and 2009. Only nine RCTs involving 424 patients were identified. These studies indicated that oral and subcutaneous morphine have similar efficacy to epidural morphine. Advantages in terms of efficacy and dose reduction were seen with the addition of local anaesthetics, ketamine, or clonidine to epidural or intrathecal infusions; fewer side-effects were seen with intrathecal administration in the only RCT that compared this route with comprehensive medical management. Owing to many methodological flaws, the evidence provided by all these RCTs can be rated only as being of very low quality.

Recommendation for spinal route of opioid administration

The data permit a weak recommendation that spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered for patients in whom analgesia is inadequate or who have intolerable adverse effects despite the optimal use of oral and parenteral opioids and non-opioid agents.

Discussion

The guidelines we present are the product of an international European Palliative Care Research Collaborative project aimed at revising previous EAPC recommendations for use of opioids to treat cancer pain.[7] We used a stepwise process[8,9] combined with a systematic literature review strategy. In view of the long-standing experience with opioid analgesics, the overall poverty of the evidence underlying many features of their use is surprising.

The quality and the content of the most recent evidence suggests that publication bias needs to be taken into account. In fact, data on different step III opioids, transdermal opioids, treatments for breakthrough pain, constipation, and neuropathic pain derived almost entirely from RCTs sponsored by the pharmaceutical industry. The lack of studies directly comparing different first-choice step III opioids is a clear example of such bias.

We did not assess pharmacoeconomic features. In some cases it can be difficult to balance the clinical benefit, which is the basis for the recommendation, and the high costs of new drugs compared with cheaper, older, and less-effective drugs, such as in case of rapid-onset opioid analgesic formulations for breakthrough pain, opioid antagonists for constipation, and others. We are, however, deeply aware of the responsibility to contain the cost of health care and of the potential for opportunity cost in the use of expensive formulations of analgesics. Socially responsible care demands that these guidelines should be a basis for decision making that will also take into consideration affordability for individual patients and at a societal level.[92] We underline that the recommendations are formulated under several stipulations, as described, and should be taken as a whole. We strongly discourage the use of any part of the text or individual recommendations alone.

The European Palliative Care Research Collaborative project has also highlighted the lack of consensus regarding methods for assessment and classification of cancer pain.[93] These differences have contributed to suboptimum treatment of and research into cancer pain[94] because of a lack of knowledge of the effects of pain characteristics on the efficacy of opioid analgesia.

The assessment of the available limited evidence in this field can be used to identify several research questions. The potential clinical effects of new pharmacological developments (eg, tapentadol or combined oxycodone and naloxone) need further research and continuous updating of the guidelines is required.

Finally, the status of the EAPC opioid recommendations can be seen as an improvement from previous standards and is proposed as a general framework to enable professionals, health-care authorities, and societies to make informed decisions with the final scope of improving the quality of life for all patients afflicted by cancer pain.

Contributors

AC was chair of the European Palliative Care Research Collaborative (EPCRC) work-package, which developed the guidelines project, identified the content, reached an expert consensus on the guidelines, and assigned the individual literature reviews. He assessed the results of these reviews and formulated the final recommendations. AC, GH, and SK wrote the final article. GH and SK were also members of the work-package and of the writing committee. SK was coordinator of the EPCRC

project. AP, CB, and FDeC were members of the EPCRC opioid guidelines work-package. MIB, CB, NC, OD, MF, MH, GJ, SK, PK, EAL, MM, SM, MN, AP, LR, CR, PS, PCS, DT, and GZ did the individual systematic literature reviews and contributed to the final guidelines version, in formulating the recommendations, revising and editing the final text. DFH was coordinator assistant of the EPCRC project. All panel members contributed to the final text version.

Conflicts of interest

AC received institutional research grants from Grunenthal, Cephalon, Novartis, Pfizer, and Mundipharma, and honoraria for lecturing or expert board membership from Cephalon, Molteni Farmaceutici, Prostrakan, and Nycomed. GH received honoraria for teaching and consultancy from Prostakan Italia, Napp, Ethypharm, and Wyeth. SK received honoraria for teaching and consultancy from Nycomed, Grunenthal Italy, Cephalon, and Archimedes. MIB received honoraria and consultancy fees from Cephalon, Grunenthal, and Pfizer. CB received consultancy fees from Molteni Pharmaceuticals. OD received honoraria for lectures from Nycomed, MH received honoraria for teaching and consultations and research grants from Mundipharma, Menarini, Nycomed, and Pfizer. MF received grants from Pfizer, Mundipharma, Cephalon, and Archimedes. PK received honorarium for lecturing from Mundipharma. MM received teaching honorarium from Cephalon. SM received honoraria, consultancy fees, and research grants from Nycomed, Prostrakan, Grunenthal, Mundipharma, Molteni, Cephalon, and Pfizer. MN received honorarium for lecture from Cephalon. CR received an honorarium from Nycomed for lecturing. GZ received honoraria, consultancy fees, and research grants from Archimedes Pharma Ltd, Cephalon UK, Pfizer, Napp Pharmaceuticals, ProStrakan, Nycomed, Dompè, and MEDA. The other authors declare they have no conflicts of interest.

Acknowledgments

This article was endorsed by the Board of Directors of the European Association for Palliative Care (EAPC). This work was partly funded by the European Palliative Care Research Collaborative (EPCRC) through the EU Sixth Framework Programme, contract no 037777, the Floriani Foundation of Milan, and by the Italian Association for Cancer Research (AIRC; grant IG 9347).

References

1 Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987; **59:** 850–56.

2 Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 2008; **19:** 1985–91.

3 WHO. Cancer pain relief, 2nd edn. Geneva: World Health Organization, 1996.

4 Cherny NI, Baselga J, De Conno F, Radbruch L. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative. *Ann Oncol* 2010; **21:** 615–26.

5 Caraceni A, Brunelli C, Martini C, Zecca E, De Conno F. Cancer pain assessment in clinical trials. A review of the literature (1999–2002). *J Pain Symptom Manage* 2005; **29:** 507–19.

6 Expert Working Group of the European Association for Palliative Care. Morphine in cancer pain: modes of administration. *BMJ* 1996; **312:** 823–26.

7 Hanks GW, De Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; **84:** 587–93.

8 Caraceni A, De Conno F, Kaasa S, Radbruch L, Hanks G. Update on cancer pain guidelines. *J Pain Symptom Manage* 2009; **38:** e1–3.

9 Pigni A, Brunelli C, Gibbins J, et al. Content development for EUROPEAN GUIDELINES on the use of opioids for cancer pain: a systematic review and Expert Consensus Study. *Minerva Anestesiol* 2010; **76:** 833–43.

10 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

11 Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008; **336:** 995–98.

12 Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ* 2008; **336:** 1049–51.

13 Guyatt GH, Oxman AD, Kunz R, et al. Incorporating considerations of resources use into grading recommendations. *BMJ* 2008; **336:** 1170–73.

14 Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliat Med* 2011; **25:** 402–09.

15 Tassinari D, Drudi F, Rosati M, Tombesi P, Sartori S, Maltoni M. The second step of the analgesic ladder and oral tramadol in the treatment of mild to moderate cancer pain: a systematic review. *Palliat Med* 2011; **25:** 410–23.

16 Klepstad P, Kaasa S, Borchgrevink PC. Starting step III opioids for moderate to severe pain in cancer patients: dose titration: a systematic review. *Palliat Med* 2011; **25:** 424–30.

17 Stone P, Minton O. European Palliative Care Research collaborative pain guidelines. Central side-effects management: what is the evidence to support best practice in the management of sedation, cognitive impairment and myoclonus? *Palliat Med* 2011; **25:** 431–41.

18 Laugsand EA, Kaasa S, Klepstad P. Management of opioid-induced nausea and vomiting in cancer patients: systematic review and evidence-based recommendations. *Palliat Med* 2011; **25:** 442–53.

19 King SJ, Reid C, Forbes K, Hanks G. A systematic review of oxycodone in the management of cancer pain. *Palliat Med* 2011; **25:** 454–70.

20 Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. *Palliat Med* 2011; **25:** 471–77.

21 Tassinari D, Drudi F, Rosati M, Maltoni M. Transdermal opioids as front line treatment of moderate to severe cancer pain: a systemic review. *Palliat Med* 2011; **25:** 478–87.

22 Cherny N. Is oral methadone better than placebo or other oral/transdermal opioids in the management of pain? *Palliat Med* 2011; **25:** 488–93.

23 Dale O, Moksnes K, Kaasa S. European Palliative Care Research Collaborative pain guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review. *Palliat Med* 2011; **25:** 494–503.

24 Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. *Palliat Med* 2011; **25:** 504–15.

25 Zeppetella G. Opioids for the management of breakthrough cancer pain in adults: a systematic review undertaken as part of an EPCRC opioid guidelines project. *Palliat Med* 2011; **25:** 516–24.

26 King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med* 2011; **25:** 525–52.

27 Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. *Palliat Med* 2011; **25:** 553–39.

28 Kurita GP, Kaasa S, Sjogren P, European Palliative Care Research Collaborative (EPCRC). Spinal opioids in adult patients with cancer pain: a systematic review: a European Palliative Care Research Collaborative (EPCRC) opioid guidelines project. *Palliat Med* 2011; **25:** 560–77.

29 Radbruch L, Trottenberg P, Elsner F, Kaasa S, Caraceni A. Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: an EPCRC opioid guidelines project. *Palliat Med* 2011; **25:** 578–96.

30 Fallon MT, Laird BJ. A systematic review of combination step III opioid therapy in cancer pain: an EPCRC opioid guideline project. *Palliat Med* 2011; **25:** 597–603.

31 Hanna M. The effect of liver impairment on opioids used to relieve pain in cancer patients. *Palliat Med* 2011; **25:** 604–05.

32 Nabal M, Librada S, Redondo M, Pigni A, Brunelli C, Caraceni A. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO step III opioids in the control of pain in advanced cancer. A systematic review of the literature. *Palliat Med* 2011; published online Nov 29. DOI:10.1177/0269216311428528.

33 Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev* 2011; **1:** CD003448.

34 Chary S, Goughnour BR, Moulin DE, Thorpe WR, Harsanyi Z, Darke AC. The dose-response relationship of controlled-release codeine (Codeine Contin) in chronic cancer pain. *J Pain Symptom Manage* 1994; **9:** 363–71.

35 Rodriguez RF, Bravo LE, Castro et al. Incidence of weak opioids adverse events in the management of cancer pain: a double-blind comparative trial. *J Palliat Med* 2007; **10:** 56–60.

36 Wilder-Smith CH, Schimke J, Osterwalder B, Senn HJ. Oral tramadol, a μ-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol* 1994; **5:** 141–46.

37 Maltoni M, Scarpi E, Modonesi C, et al. A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. *Support Care Cancer* 2005; **13:** 888–94.

38 Marinangeli F, Ciccozzi A, Leonardis M, et al. Use of strong opioids in advanced cancer pain: a randomized trial. *J Pain Symptom Manage* 2004; **27:** 409–16.

39 Mercadante S, Salvaggio L, Dardanoni G, Agnello A, Garofalo S. Dextropropoxyphene versus morphine in opioid-naive cancer patients with pain. *J Pain Symptom Manage* 1998; **15:** 76–81.

40 Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev* 2007; **4:** CD003868.

41 Reid CM, Martin RM, Sterne JA, Davies AN, Hanks GW. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166:** 837–43.

42 Hanna M, Thipphawong J, the 118 study group. A randomized, double-blind comparison of OROS® hydromorphone and controlled-release morphine for the control of chronic cancer pain. *BMC Palliat Care* 2008; **7:** 17.

43 Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain* 1986; **25:** 297–312.

44 Hoskin PJ, Hanks GW, Aherne GW, Chapman D, Littleton P, Filshie J. The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* 1989; **27:** 499–505.

45 De Conno F, Ripamonti C, Fagnoni E, et al. The MERITO study: a multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during 'titration phase' in patients with cancer pain. *Palliat Med* 2008; **22:** 214–21.

46 Klepstad P, Kaasa S, Jystad A, Hval B, Borchgrevink PC. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain* 2003; **101:** 193–98.

47 Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. *Palliat Med* 2003; **17:** 248–56.

48 Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol* 2001; **2:** 165–72.

49 Tassinari D, Sartori S, Tamburini E, et al. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. *J Palliat Med* 2008; **11:** 492–501.

50 Mercadante S, Porzio G, Ferrera P, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *Eur J Pain* 2008; **12:** 1040–46.

51 Poulain P, Denier W, Douma J, et al. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. *J Pain Symptom Manage* 2008; **36:** 117–25.

52 Nicholson AB. Methadone for cancer pain. *Cochrane Database Syst Rev* 2007; **4:** CD003971.

53 Bruera E, Palmer JL, Bosnjak S, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22:** 185–92.

54 Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. *J Pain Symptom Manage* 1986; **1:** 203–07.

55 Twycross RG. Choice of strong analgesic in terminal cancer: diamorphine or morphine? *Pain* 1977; **3:** 93–104.

56 Houde RW, Wallenstein SL, Beaver WT. Evaluation of analgesics in patients with cancer pain. Oxford: Pergamon Press, 1966.

57 Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. *J Pain Symptom Manage* 2009; **38:** 426–39.

58 Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* 2004; **3:** CD004847.

59 Ventafridda V, Spoldi E, Caraceni A, Tamburini M, De Conno F. The importance of subcutaneous morphine administration for cancer pain control. *Pain Clinic* 1986; **1:** 47–55.

60 Bruera E, Brenneis C, Michaud M, et al. Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. *Cancer* 1988; **62:** 407–11.

61 Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev* 2002; **1:** CD003447.

62 Anderson SL, Shreve ST. Continuous subcutaneous infusion of opiates at end-of-life. *Ann Pharmacother* 2004; **38:** 1015–23.

63 Grond S, Zech D, Lehmann KA, Radbruch L, Breitenbach H, Hertel D. Transdermal fentanyl in the long-term treatment of cancer pain: a prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck region. *Pain* 1997; **69:** 191–98.

64 Kornick CA, Santiago-Palma J, Khojainova N, Primavera LH, Payne R, Manfredi PL. A safe and effective method for converting cancer patients from intravenous to transdermal fentanyl. *Cancer* 2001; **92:** 3056–61.

65 Mercadante S, Villari P, Ferrera P, Casuccio A, Fulfaro F. Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion. *Cancer* 2002; **95:** 203–08.

66 Zech DF, Grond SU, Lynch J, Dauer HG, Stollenwerk B, Lehmann KA. Transdermal fentanyl and initial dose-finding with patient-controlled analgesia in cancer pain. A pilot study with 20 terminally ill cancer patients. *Pain* 1992; **50:** 293–301.

67 Elsner F, Radbruch L, Loick G, Gartner J, Sabatowski R. Intravenous versus subcutaneous morphine titration in patients with persisting exacerbation of cancer pain. *J Palliat Med* 2005; **8:** 743–50.

68 Takahashi M, Ohara T, Yamanaka H, Shimada A, Nakaho T, Makoto Y. The oral-to-intravenous equianalgesic ratio of morphine based on plasma concentrations of morphine and metabolites in advanced cancer patients receiving chronic morphine treatment. *Palliat Med* 2003; **17:** 673–78.

69 Ferrell BR, Nash CC, Warfield C. The role of patient-controlled analgesia in the management of cancer pain. *J Pain Symptom Manage* 1992; **7:** 149–54.

70 Bruera E, Brenneis C, Michaud M, MacMillan K, Hanson J, MacDonald RN. Patient-controlled subcutaneous hydromorphone versus continuous subcutaneous infusion for the treatment of cancer pain. *J Natl Cancer Inst* 1988; **80:** 1152–54.

71 Vanier MC, Labrecque G, Lepage-Savary D, Poulin E, Provencher L, Lamontagne C. Comparison of hydromorphone continuous subcutaneous infusion and basal rate subcutaneous infusion plus PCA in cancer pain: a pilot study. *Pain* 1993; **53:** 27–32.

72 Citron ML, Johnston-Early A, Boyer M, Krasnow SH, Hood M, Cohen MH. Patient-controlled analgesia for severe cancer pain. *Arch Intern Med* 1986; **146:** 734–36.

73 Swanson G, Smith J, Bulich R, New P, Shiffman R. Patient-controlled analgesia for chronic cancer pain in the ambulatory setting: a report of 117 patients. *J Clin Oncol* 1989; **7:** 1903–08.

74 Meuret G, Jocham H. Patient-controlled analgesia (PCA) in the domiciliary care of tumour patients. *Cancer Treat Rev* 1996; **22** (suppl A)**:** 137–40.

75 Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G, Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009; **13:** 331–38.

76 Haugen DF, Hjermstad MJ, Hagen N, Caraceni A, Kaasa S, European Palliative Care Research Collaborative (EPCRC). Assessment and classification of cancer breakthrough pain: a systematic literature review. *Pain* 2010; **149:** 476–82.

77 Zeppetella G, Ribeiro MD. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev* 2006; **1:** CD004311.

78 Mercadante S, Villari P, Ferrera P, Casuccio A, Mangione S, Intravaia G. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. *Br J Cancer* 2007; **96:** 1828–33.

79 Mercadante S, Radbruch L, Davies A, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. *Curr Med Res Opin* 2009; **25:** 2805–15.

80 Kress HG, Oronska A, Kaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 µg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clin Ther* 2009; **31:** 1177–91.

81 Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain* 2006; **22:** 805–11.

82 Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol* 2007; **5:** 327–34.

83 Mercadante S, Villari P, Casuccio A. An Italian survey on the attitudes in treating breakthrough cancer pain in hospice. *Support Care Cancer* 2011; **19:** 979–83.

84 Weinstein SM, Messina J, Xie F. Fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer pain: a long-term, open-label safety study. *Cancer* 2009; **115:** 2571–79.

85 Mercadante S, Intravaia G, Villari P, Ferrera P, Riina S, Mangione S. Intravenous morphine for breakthrough (episodic-) pain in an acute palliative care unit: a confirmatory study. *J Pain Symptom Manage* 2008; **35:** 307–13.

86 Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol* 2009; **7:** 39–46.

87 Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008; **358:** 2332–43.

88 Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. *J Pain Symptom Manage* 2008; **35:** 458–68.

89 Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. *Palliat Med* 1996; **10:** 135–44.

90 McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev* 2005; **1:** CD005180.

91 American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 2009; **57:** 1331–46.

92 Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *BMJ* 1999; **318:** 527–30.

93 Kaasa S, Apolone G, Klepstad P, et al; European Palliative Care Research Collaborative (EPCRC) and the European Association for Palliative Care Research Network (EAPC RN). Expert conference on cancer pain assessment and classification—the need for international consensus: working proposals on international standards. *BMJ Support Palliat Care* 2011; **1:** 281–87.

94 Kaasa S, Loge JH, Fayers P, et al. Symptom assessment in palliative care: a need for international collaboration. *J Clin Oncol* 2008; **26:** 3867–73.