Use of Opioid Analgesics in the Treatment of Cancer Pain: Evidence-based Recommendations from the EAPC

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EVIDENCE-BASED RECOMMENDATIONS FROM THE EAPC

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A project of the European Palliative Care Research Collaborative (EPCRC)
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ABSTRACT

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 a 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.

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, in which the choice of analgesic is determined by the severity of the pain [3]. The WHO method has been adopted worldwide but the lack of up-to-date evidence, knowledge, and opioid availability has obstructed the path to effective relief of cancer pain [2,4].

Randomized 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. The results were presented at the Fifth Bristol Opioids Conference, Bristol, UK, Feb8-9, 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 [33] review and 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 judgements 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.

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

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 demonstrated 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 a 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 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.

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

Oral opioid	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

WHO step III opioid of first choice

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 significantly 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 difference 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

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

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 of them 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

Methadone has often been considered 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 literature 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 who 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 2 (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. The use of 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

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 a recently 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 rate 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

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 both 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.

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.

Table 2: Relative analgesic ratios for opioid switching

	RELATIVE ANALGESIC RATIO	STRENGTH OF THE RECOMMENDATION FOR USE
Oral morphine to oral oxycodone	1.5 : 1	Strong
Oral oxycodone to oral hydromorphone	4 : 1	Strong
Oral morphine to oral hydromorphone	5 : 1	Weak
Oral morphine to TD buprenorphine (*)	75 : 1	Weak
Oral morphine to TD fentanyl (**)	100 : 1	Strong

(*) 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).
TD=transdermal.

Alternative systemic routes of opioid administration

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 hour with intravenous administration in most patients [47].

The relative potency 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

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 intranasl 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 these 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].

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

	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)	70% (INF)	90% (INF)
			20% (OTFC)	40% (OTFC)	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)

(*) 33% pain reduction from baseline
RCT=randomised controlled trial
INF=intranasal fentanyl
OTFC=oral transmucosal fentanyl
FBT=fentanyl buccal tablets

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 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

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

Prophylactic laxative treatment is frequently given to patients on long-term opioid therapy. The Cochrane systematic literature 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 demonstrated 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

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

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

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. A more recent 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 in the high-risk elderly population, because of these drugs' known gastrointestinal, renal, and cardiovascular toxic effects [91].

All of 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)

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 adverse events unless careful titration of both drugs is undertaken.

The spinal route of opioid administration

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 term 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.

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 reference lists of identified papers.

Contributors

Augusto Caraceni 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. Augusto Caraceni, Geoffrey Hanks, and Stein Kaasa wrote the final article. **Geoffrey Hanks** and **Stein Kaasa** were also members of the work-package and of the writing committee. **Stein Kaasa** was coordinator of the EPCRC project.

Alessandra Pigni, **Cinzia Brunelli,** and **Franco De Conno** were members of the EPCRC opioid guidelines work-package. **Michael I. Bennett**, **Cinzia Brunelli**, **Nathan Cherny**, **Ola Dale**, **Marie Fallon**, **Magdi Hanna**, **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** and **Giovambattista Zeppetella** did the individual systematic literature reviews and contributed to the final guidelines version, in formulating the recommendations, revising and editing the final text. **Dagny Faksvåg Haugen** was Project Executive Officer of the EPCRC project. All panel members contributed to the final text version.

Conflicts of interest

Augusto Caraceni 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. **Geoffrey Hanks** received honoraria for teaching and consultancy from Prostakan Italia, Napp, Ethypharm, and Wyeth. **Stein Kaasa** received honoraria for teaching and consultancy from Nycomed, Grunenthal Italy, Cephalon, and Archimedes. **Michael I. Bennett** received honoraria and consultancy fees from Cephalon, Grunenthal, and Pfizer. **Cinzia Brunelli** received consultancy fees from Molteni Pharmaceuticals. **Ola Dale** received honoraria for lectures from Nycomed, **Magdi Hanna** received honoraria for teaching and consultations and research grants from Mundipharma, Menarini, Nycomed, and Pfizer. **Marie Fallon** received grants from Pfizer, Mundipharma, Cephalon, and Archimedes. **Pål Klepstad** received honorarium for lecturing from Mundipharma. **Marco Maltoni** received teaching honorarium from Cephalon. **Sebstiano Mercadante** received honoraria, consultancy fees, and research grants from Nycomed, Prostrakan, Grunenthal, Mundipharma, Molteni, Cephalon, and Pfizer. **Maria Nabal** received honorarium for lecture from Cephalon. **Colette Reid** received an honorarium from Nycomed for lecturing. **Giovambattista Zeppetella** 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.

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