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

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Developed on behalf of the European Palliative Care Research Collaborative

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A project of the European Palliative Care Research Collaborative (EPCRC)
on behalf of the
European Association for Palliative Care (EAPC)

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ABSTRACT

This document reports 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 of the guidelines was undertaken by the European Palliative Care Research Collaborative (EPCRC). Previous EAPC guidelines were reviewed and compared with other currently available guidelines by formal expert consensus and an international communication strategy. The content of the guidelines was defined according to a number of topics and each of them assigned to panellists who developed systematic literature reviews with a common methodology. The recommendations were then developed by a writing committee combining the evidence derived from the systematic reviews with the panellists' evaluation in a shared co-authorship 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 GRADE system (Grading of Recommendations Assessment, Development and Evaluation System).

INTRODUCTION

Moderate to severe pain in cancer is common, occurring in 70-80% of patients with advanced disease. We have the means and the knowledge to relieve most pain in cancer for the majority of patients [1], but there is evidence from surveys and observational studies that many patients suffer 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 current clinical practice. The analgesic ladder is the central idea of the WHO guidelines on cancer pain relief (WHO 1996), 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, lack of knowledge, and lack of opioid availability have obstructed the path to effective cancer pain relief [2,4].

Randomized controlled trials (RCTs) in the cancer pain patient population are beset by particular difficulties [5]. In the absence of hard evidence from RCTs, expert consensus and clinical guidelines may be particularly helpful, because cancer pain relief is a specialist area where 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]. An update was published in 2001 [7]. The aim of the present work in updating the EAPC recommendations was to strengthen their scope by applying a rigorous evidence-based methodology, and a wide international development process.

METHODS

Guidelines development methodology

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 formalized expert consensus process that led to 30 practical clinical questions being summarised in 22 topics [8,9]. The subsequent guidelines development process followed the GRADE system [10-13].

Each of the 22 topics was assigned to a group of collaborators who carried out a systematic review according to a standardised method. The results were presented at an international meeting in the UK (the 5th Bristol Opioids Conference, February 2010) and 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.

The literature review on the treatment of opioid-related constipation completely overlapped with a Cochrane [33] review and was not submitted for publication.

Sixteen 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 EPCRC, the Board of Directors of the EAPC and to each collaborator (reviewer) 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.

A more comprehensive description of the methodology is available online.

THE EAPC RECOMMENDATIONS

WHO step II opioids

Step II opioids (table 1) have been traditionally used for moderate cancer pain. The systematic review of the literature [15] showed that codeine and tramadol are effective compared with placebo. The additive analgesic effect of paracetamol in conjunction with codeine was demonstrated in an RCT [34] comparing codeine alone vs codeine + paracetamol which showed that 60/600 mg codeine/paracetamol four times a day was as effective and safe as 150 mg codeine two times a day.

There was only one RCT providing direct comparative data for the step II opioids and that study [35] showed no difference in efficacy between tramadol, codeine + paracetamol and hydrocodone + paracetamol; however, tramadol produced more side effects. 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 in the WHO method has been addressed in three trials [37-39] 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 some patients may achieve better pain relief than by using Step II drugs. There is no evidence that initiating opioid therapy by using a step II drug constitutes a better overall management of cancer pain, but the same was found for step III drugs (Table 1).

RECOMMENDATION

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	Alone or in combination with paracetamol. Daily doses ≥ 360 mg not recommended
Tramadol	Alone or in combination with paracetamol. Daily doses ≥ 400 mg not recommended
Hydrocodone	Used as a substitute for codeine in some countries
Oxycodone	When used at low doses (such as ≤ 20 mg/day) Alone or in combination with paracetamol
Morphine	When used at low doses (such as ≤ 30 mg/day)
Hydromorphone	When used at low doses (such as ≤ 4 mg/day)

(*) Originally classified as weak opioids

WHO step III opioid of first choice

Morphine is the prototype opioid analgesic and oral morphine has been considered for 25 years 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.

In recent years there have been many developments of novel formulations of 'old' opioids such as oxycodone, hydromorphone and fentanyl 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]; there is one systematic review of oxycodone updating an earlier review and meta-analysis [19], and one review of hydromorphone [20]. These reviews included nine randomized trials comparing oral administration of morphine, oxycodone and hydromorphone, involving a total of 654 patients. Of these, eight were designed as superiority trials and seven of them showed no significant differences in efficacy. Similar results were reported in the only meta-analysis of four studies comparing oxycodone with morphine or hydromorphone [41]. One unpublished trial [40] showed a slight statistically significant difference in favour of morphine compared with hydromorphone. One trial demonstrated equivalence for morphine and hydromorphone [42]. The comparison of the tolerability profiles of the three opioids did not show consistent differences.

The indirectness and quality 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

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 use of immediate-release oral morphine every four hours in initiating morphine administration was not based on controlled clinical trials but on a long-standing practice, based on the pharmacokinetic profile of this formulation (t_{max} < 1h; $t_{1/2\beta}$ 2-3h; duration of effect about 4 h) [43,44]. Individualisation of the dose of opioid is achieved by starting low and titrating to effect [45]. With the introduction of oral and transdermal slow release opioids, clinicians were encouraged initially to titrate the dose using the immediate-release opioid and then switch to the modified-release preparation [6]. 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 initiating treatment with oral opioids in the patient's home, and have found this to work well.

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

RECOMMENDATION

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 (TD) fentanyl and buprenorphine delivery systems build slowly drug plasma levels with very long apparent half-lives (several days) and a prolonged latency to reach pharmacological steady states [48]. The use of these preparations as a first choice step III opioid or as an alternative to step II has been debated. The use of transdermal fentanyl and buprenorphine requires that titration is performed according to the apparent drug half-life, i.e. every three days using in the interim immediate-release opioids.

A systematic review of transdermal fentanyl and buprenorphine for moderate to severe cancer pain [21] includes the results of one meta-analysis [49] carried out on four RCTs comparing oral morphine with fentanyl or buprenorphine and one RCT with three parallel arms comparing 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 observed for constipation, and patients' preference [49], suggesting that in some cases transdermal opioids may be appropriate and effective in patients who have not previously received step III opioids [50].

None of these trials were blinded, some were of low methodological quality and two of them were carried out on patients already taking step III opioids. Consequently, the evidence on this topic is low level and partly indirect.

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

RECOMMENDATION
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 with a very long and unpredictable half-life [43] require carefully individualized dosing

schedules. Oral methadone is the most frequently considered option in the practice of opioid switching. From the systematic literature review by the Cochrane collaboration [52], updated to July 2009 by Cherny [22], only three RCTs [50,53,54] involving a total of 277 patients addressed the comparison of methadone with another step III opioid (one of them had a third arm treated with TD fentanyl). There was no difference in efficacy between the drugs when compared in patients either treated with step II opioids or who were opioid naive. In one study [53], methadone was associated with a higher incidence of sedation, resulting in a higher percentage of patients dropping out because of adverse effects. In a previous study [55], 4/26 vs 2/26 in the methadone and diamorphine + cocaine groups, respectively, withdrew because of sedation.

Although methodological limitations were found in these three studies, data consistently show no significant differences in methadone analgesic efficacy when compared to 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
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 may be explained pharmacologically by the phenomenon of incomplete cross tolerance [56,57]. A Cochrane review [58] and a recently updated systematic review [23] failed to identify any randomized trial supporting the practice of opioid switching. The available uncontrolled trials, in the Quigley review, report on 399 patients, and 280 additional patients were added in the more recent review [23,58]. The two reviews show that opioid switching is more often performed when pain is not well controlled and side effects are limiting dose escalation, than when pain is just not controlled with tolerable side effects. 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

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.

Opioid relative analgesic potency

The practice of switching from one opioid drug to another due to unsatisfactory analgesia requires that the new drug is prescribed in a dose that is both safe and efficacious. Equipotency dose calculations which produced the first equianalgesic tables [57] were obtained in cross-over studies and with acute dose administrations in patients with low or no previous exposure to the opioid under study.

The practical equianalgesic dose ratios offered more recently are instead derived either from RCTs, aiming at comparing the efficacy of two drugs, or from observational case series describing the practice of opioid switching during chronic administration. The review by Mercadante and Caraceni [24] addressed specifically the evidence derived from six randomized controlled cross-over trials and 26 case series. The most robust data come from patients stabilized 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, although high quality, case series [24]. The evaluation of 26 case series shows that the variability due to the reasons for switching (i.e. poor analgesia and/or opioid related side effects), pre-switching opioid titration, and overall opioid exposure, makes the conversion ratios 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 to start the second opioid at a dose which is 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 and 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

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

OPIOID SWITCH	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 of oral morphine $\equiv$ TD buprenorphine 35 μg/h ($\equiv$ 0.8 mg in 24 h)
(**) Example: 60 mg of oral morphine $\equiv$ TD fentanyl 25 μg/h ($\equiv$ 0.6 mg in 24 h)
TD=transdermal

Alternative systemic routes of opioid administration

Parenteral opioid administration may be necessary for patients who cannot swallow, patients with nausea and vomiting, or patients at the end of life who are unable to continue with oral medication because of weakness or debility [59,60]. A systematic literature review [29] found 18 studies comparing different routes of administration for cancer pain control. In addition 3 systematic reviews were considered relevant to the topic [40,61,62].

Subcutaneous infusion

Four studies compared subcutaneous (SC) and intravenous (IV) opioid infusions, but only one was a high quality double-blind double dummy cross-over trial, including 99 patients. These studies show similar efficacy and tolerability with SC and IV administration and no difference in the dose used, but with faster

Use of Opioid Analgesics in the Treatment of Cancer Pain
Evidence-based Recommendations from the EAPC. Feb 2012

onset of pain relief using the IV route. These results were confirmed in four studies sequentially switching from IV to SC administration. In one of the studies, patients who had received high doses IV, needed an increased SC dose. The remaining studies reported on more than 1100 patients and were uncontrolled observational studies.

Intravenous administration

IV administration has been considered for rapid titration in cases of severe unrelieved pain [63-66] and compared with SC infusion [67]. In one study IV titration with 1.5 mg of morphine every 10 minutes was compared with oral morphine titration (5 to 10 mg) every 4 hours. Pain control could be achieved within 1 hour in most patients with IV administration [47].

The oral to IV relative potency ratio for morphine in patients with cancer pain receiving chronic morphine treatment was evaluated to be 2.9 [68]. The ratio is similar for oral to SC morphine.

Rectal administration

Rectal morphine administration was investigated in two RCTs in comparison with oral and SC administration demonstrating similar pain relief and faster onset of effect with rectal administration [29].

Patient-controlled analgesia (PCA)

The use of IV or SC opioid infusion with PCA has been investigated in few studies [69], including two non-blind controlled trials [70,71] and a number of uncontrolled case series [72-74].

RECOMMENDATION

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 BTP to transitory exacerbations of pain that occur on a background stable pain that is 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 randomized controlled trials of opioid medications involving new preparations of transmucosal fentanyl: oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT) and intranasal fentanyl (INF). In all studies the patient populations were already exposed to variable doses of systemic opioids at doses >/= 60 mg of oral morphine. These studies proved that OTFC, FBT and INF are all superior to placebo in treating BTP and that OTFC is more effective than immediate release oral morphine. Unblinded comparisons show that IV morphine is superior to OTFC in the first 15 minutes but this difference is no longer evident at 30 minutes after administration [78] and that INF provides a faster onset of analgesia than OTFC. By comparing the different study results, and with some limitations associated with the study quality, it is possible to summarize the time course of analgesia obtainable from different fentanyl preparations (Table 3) [79-82].

No simple relationship could be demonstrated in the RCTs between the effective dose of OTFC, FBT and INF and the 24hr 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 higher than the lowest recommended dose for patients who are on high doses of opioids.

Most of these studies reported adverse events that included expected opioid-related side effects such as sedation and dizziness as a potential limitation to the titration to an effective dose of OTFC, FBT and INF. The local mucosal tolerability was good but some cases of local ulcer have been reported and long-term data on prolonged use are limited [84]. Intravenous opioid titration and bolus administration have also been used for improving breakthrough pain control [29,85].

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

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

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

RECOMMENDATION

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 preemptively predictable episodes of breakthrough pain in the 20–30 min preceding the provoking manoeuvre.

Treatment of opioid-related emesis

Opioid-induced nausea and/or vomiting are experienced by up to 40% of cancer patients with no prior emesis. Since nausea/vomiting is not an invariable consequence of opioid administration, prophylactic antiemetic medication is not usually prescribed.

The systematic review by Laugsand et al. [18] identified nine studies in which relief of nausea/vomiting due to opioids was the primary outcome. Only two RCTs demonstrated efficacy, which was achieved with high doses of metoclopramide.

Fifty studies of relatively lower quality included nausea and/or vomiting as secondary outcomes and suggested also the potential usefulness of dose reduction, switching from one opioid to another, or changing the route of administration, from oral to transdermal or parenteral.

RECOMMENDATION
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 often given to patients on long-term opioid therapy. The Cochrane systematic literature analysis [33] reviewed seven RCTs, with a total of 616 patients. Four of the studies compared different kinds of laxatives (codanthramer vs senna; lactulose + senna vs magnesium hydroxide + liquid paraffin; senna vs lactulose; mishrakanesham, an ayurvedic formulation, vs senna) but did not demonstrate significant differences between them. Three RCTs demonstrated that methylnaltrexone is effective in reversing opioid-related constipation as confirmed also by a meta-analysis [33]. The success rate is about 50%. The administration of methylnaltrexone has been associated with flatulence and dizziness [86,87]. Abdominal cramping was reported in a dose related fashion [86,88], but due 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 [89] studied oral naloxone to correct opioid-related constipation but showed no efficacy.

RECOMMENDATION

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

Sedation

Four different drugs were identified to treat opioid-induced sedation (methylphenidate, donepezil, dexamphetamine, iv caffeine) in eleven publications. Methylphenidate administration was evaluated in three RCTs: two gave positive results and one was negative, but the quality of the last study was lower. A number of side effects were also associated with the use of methylphenidate (anxiety, hallucinations and sweating). The quality of the studies involving dexamphetamine, caffeine and donepezil was not sufficient to make any recommendation about their use.

Myoclonus

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

Cognitive impairment

Two RCTs compared methylphenidate or caffeine with placebo showing improvement on cognitive and psychomotor performance in patients during long-term opioid therapy.

RECOMMENDATION

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 renal failure

Particular precautions in the administration of opioids in cancer patients with impaired renal function has been the object of a number of guidelines, expert opinions, and interpretations, based on known opioid pharmacokinetics which may result in the accumulation of the parent drug and its metabolites in patients with renal failure.

The systematic literature review by King et al.[26] could identify 15 studies reporting specifically on clinical outcomes relevant to the use of opioids for cancer pain in patients with renal impairment; eight prospective observational trials and seven retrospective studies. All these studies are 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 renal failure is not consistent. The present recommendation is therefore based on general caution criteria and indirect pharmacological evidence.

RECOMMENDATION

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 and/or non-steroidal anti-inflammatory drugs (NSAIDs) without opioids. Paracetamol and NSAIDs are also included in combination with opioids as part of step II and step III. This recommendation is limited to the use of these drugs in combination with step III opioids.

The Cochrane review updated to March 2003 [90] identified 42 eligible trials. The evidence from this review supported the superiority of NSAIDs and paracetamol to placebo, while no difference could be found in comparing 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 new articles giving a total of 12 eligible studies, seven of NSAIDs and five of paracetamol. Three studies demonstrated increased analgesia and two a decrease in opioid consumption with NSAID and opioid combination treatments. In one study a mean difference of 0.4 on a 0-10 numerical pain intensity rating scale in favour of paracetamol was found. One study showed a higher prevalence of GI side effects in NSAIDs treated patients. In general, trial design and duration of reviewed studies do not allow an adequate evaluation of the side effects of prolonged use of NSAIDs in this population, but caution is recommended, with particular attention to the high-risk elderly population, due to these drugs' known gastrointestinal, renal, and cardiovascular toxic effects [91].

All of these studies suffer from significant limitations due to the heterogeneity of design, patient population, and outcome measures used and the lack of long term evaluation.

RECOMMENDATION

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 adjuvant drugs for neuropathic pain most frequently used are tricyclic antidepressants such as amitriptyline and imipramine, and antiepileptics such as gabapentin and pregabalin. A systematic literature review, specifically addressing this topic, identified five RCTs [27]. A definition of neuropathic cancer pain was available in all of them but it was inconsistent across the studies. Only two trials were placebo controlled, one of gabapentin and the other of amitriptyline, both as add-on therapy to opioid analgesics. Both studies demonstrated an additional analgesic effect on pain intensity. Pain relief was associated with adverse events usually as an increase of CNS side effects; in particular somnolence and dizziness, with one case of respiratory depression.

RECOMMENDATION

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 for 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 using this type of administration and the opportunity to add specific adjuvant drugs may be beneficial for patients with insufficient analgesia and/or significant side effects due to systemic opioid administration. The use of other spinal agents not involving the administration of spinal opioids was not considered in this recommendation.

The literature search conducted by Kurita et al. [28] identified 42 relevant articles published between 1982 and 2009. Only nine randomized controlled trials were identified for an overall total of 424 patients. 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, and less side effects favoured the intrathecal

administration in the only comparison RCT between intrathecal and comprehensive medical management. Due to many methodological flaws the evidence provided by all these RCTs can be rated only of very low quality.

RECOMMENDATION

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

These guidelines are the product of a European international project (EPCRC) aimed at revising previous EAPC recommendations on the use of opioids in cancer pain [7]. We have used an international stepwise process [8,9] combined with a systematic literature review strategy. Considering the long standing experience with opioid analgesics, the overall poverty of the evidence underlying many aspects of their use is surprising.

The quality and the content of the most recent evidence included in these guidelines suggest that also publication bias needs to be taken into account. In fact, data on the comparison of different opioids (Recommendations 2, 4 and 5), on new drugs for BTP (Recommendation 9), for treating constipation (Recommendation 11), and neuropathic pain (Recommendation 15) were produced almost entirely by RCTs sponsored by the pharmaceutical industry. The lack of studies directly comparing different first choice step III opioids is a clear example of this bias.

Pharmacoeconomic considerations were not included in these guidelines. In some cases it can be difficult to balance the clinical benefit, which is the basis for the recommendation, and the higher costs of new drugs compared with cheaper and older, less effective drugs, such as in case of rapid-onset opioid analgesic formulations for breakthrough pain, opioid antagonists for constipation, and others. On the other hand, even though in the absence of appropriate cost-benefit analyses, we are deeply aware of the social 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 individual patient and societal affordability [92]. We also underline that the recommendations are formulated under a number of stipulations as described, and should not be used in isolation without the whole accompanying text. The use of part of the text or even of the single recommendation alone, without the accompanying text, is discouraged.

The EPCRC 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] due to a lack of knowledge on the impact of pain characteristics on the efficacy of opioid analgesia.

The evaluation of the available limited evidence in this field can be used to identify a number of research questions. The potential clinical impact of new pharmacological developments (such as tapentadole or oxycodone and naloxone in combination) needs also more research and continuous updating of the guidelines.

Finally, the present status of the EAPC opioid recommendations can be seen as an improvement from previous standards and is proposed as a very 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

A systematic search for all relevant outcomes associated with each topic was performed using Medline, EMBASE and the Cochrane Central Register of Controlled Trials databases, with a time frame ranging from each database set-up date to July 31st 2009. The search strategy included both text words and MeSH/EMTREE terms specifically relevant to each outcome; hand search of the reference lists of identified papers was also performed. Studies were included if they: were carried out in human, adult patients with chronic cancer pain; contained data on efficacy/and or side effects of the treatment considered; were written in English. Because of the paucity of available data for some of the topics, non-randomized trials were also considered if RCTs were not retrieved. Meta-analyses were included as independent original papers, while narrative systematic reviews were excluded.

Contributors

Augusto Caraceni was chair of the EPCRC work package which developed the guidelines project, identified the guidelines content, reached an expert consensus on them, 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 guidelines document with the contribution of all the other panel members. **Goeffrey Hanks** and **Stein Kaasa** were also members of the work package and of the writing committee. **SK** was coordinator of the EPCRC project.

The EAPC opioid guidelines panel contribution:

Alessandra Pigni, **Cinzia Brunelli** and **Franco De Conno** were members of the EPCRC opioid guidelines work package. **Michael 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** performed 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. **Goeffrey Hanks** received honoraria from Prostakan Italia, Napp, Ethypharm and Wyeth. **Stein Kaasa** received honoraria for teaching and consultancy from Nycomed, Grunenthal Italy, Cephalon and Archimedes. **Michael 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 grant 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 or research grants from Nycomed, Prostrakan, Grunenthal, Mundipharma, Molteni, Cephalon and Pfizer. **Maria Nabal** received honorarium for lecture from Cephalon. **Colette Reid** received honorarium from Nycomed for lecturing. **Giovambattista Zeppetella** received honoraria, consultancy fees or research grant from Archimedes Pharma Ltd, Cephalon UK, Pfizer, Napp Pharmaceuticals, ProStrakan, Nycomed, Dompè and MEDA. **Nathan Cherny, Franco De Conno, Dagny Faksvåg Haugen, Gitte Juhl, Samuel King, Eivor Laugsand, Alessandra Pigni, Lukas Radbruch, Per Sjøgren, Patrick C. Stone,** and **David Tassinari** have no conflict of interest to declare.

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Use of Opioid Analgesics in the Treatment of Cancer Pain
Evidence-based Recommendations from the EAPC. Feb 2012

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