REVIEW

Content development for EUROPEAN GUIDELINES on the use of opioids for cancer pain: a systematic review and Expert Consensus Study

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ABSTRACT

Workpackage 3.1 (WP 3.1), within the European Palliative Research Collaborative (EPCRC), was aimed at critically revising and updating the European Association for Palliative Care recommendations on cancer pain management. The aim of this paper is to report the results of the first phase in the revision process which consists of a literature review and an expert consensus about the contents to be considered relevant in the development of the new guidelines. A systematic literature search was carried out from 2001 to 2008 through various databases including Medline, Cinahl, Cochrane Database of Systematic Reviews, Embase and Google. Through this process, guideline quality was evaluated, content was compared with EAPC recommendations and a first set of key-points was developed. A modified two-round Delphi method was applied to choose the most relevant topics for future systematic literature reviews. Fourteen guidelines on cancer pain management, published or updated after 2000, were retrieved. A comparison of these guidelines with the EAPC recommendations led to the formulation of 37 key-points, which were submitted to a panel of experts through a Delphi method. Through the responses given by the experts (25 after the first round and 19 after the second) and after a revision by the WP 3.1 local and steering committees, a final list of 22 topics was generated to answer all identified key-points. Each of these topics will be the object of systematic literature reviews. The final version of the "Evidence-based guidelines for the use of opioid analgesics in the treatment of cancer pain: the EAPC recommendations" will be based on the results of the 22 systematic literature reviews. *(Minerva Anestesiol 2010;76:833-43)*

Key words: Guidelines as topic - Neoplasms - Pain - Delphi technique - Analgesics, opioid.

Guidelines have the aim of helping caregivers and patients choose the most appropriate treatment or care modality, thus reducing the variability of care practices by using systematic interventions for crucial decisions. The evidence that cancer pain is still often undertreated can be interpreted as a result of lack of adequate clinical guidelines or a failure to properly implement and comply with the available guidelines.[1-3]

A number of guidelines for the management of

cancer pain of different sources and for different audiences are available either as published materials or online. Among the most widely used and recognized cancer pain guidelines is "Cancer pain relief" by the World Health Organization (WHO), known for their analgesic ladder based approach.[4] The European Association for Palliative Care (EAPC) guidelines on opioid analgesics in the management of cancer pain, published in 2001,[5] were seen as an evolution of the WHO recommendations as they developed in detail the role of opioids in the analgesic ladder.

The impact of the WHO and EAPC guidelines on clinical practice and patient outcomes has never been clearly demonstrated, but it is likely that they have had a profound influence.[6] Still, patients with cancer pain often have insufficient relief from therapy for two different reasons: patients have no access to appropriate treatment strategies or the available treatment strategies are not efficacious enough to adequately control pain in a particular group of patients. To improve cancer pain management, but also to highlight the needs for research into new approaches and treatment for cases not responding to standard management, it is necessary to have valid evidence-based guidelines to be known, diffused and implemented.[7]

International guidelines may have some of these favorable characteristics to obtain these results, but they need to be regularly updated.

The Workpackage 3.1 (WP 3.1) within the European Palliative Research Collaborative (EPCRC), established in 2006,[8, 9] was aimed at critically revising and updating the EAPC guidelines through the enhancement and development of new topics emerging from the most recent literature.

The first steps in this revision process included reviewing existing guidelines, describing their quality and developing a comprehensive list of relevant key points to be the object of the new guidelines. This was done by a literature review and expert consensus process. The second step is underway and will be accomplished by systematic literature reviews on each key point and the production of final guidelines. The aim of this paper is to report the results of the first phase.

Materials and methods

Guidelines search

A systematic literature search was conducted from 2001 to 2008 through various databases including Medline, Cinahl, Cochrane Database of Systematic Reviews, Embase and Google. The search strategy for Medline was: "Practice Guidelines" [Mesh], "Analgesics, Opioid" [Mesh] and "Neoplasms" [Mesh] and "Pain" [Mesh]. Similar search strings were adapted for the other databases. Only guidelines in English which were published or downloadable from the web were taken into consideration.

Initial key points list development

The structure, methods and content of all guidelines have been reviewed and compared with the EAPC guidelines. An inventory of all the key points or topics present in the guidelines examined was circulated both to the WP 3.1 local group (four members AP, AC, FDC, CB) and the steering group (five members SK, PK, LR, GH, JG) to collect comments and suggest additional key points, thus originating a first set of topics to be tested.

Guideline quality evaluation and content comparison with EAPC guidelines

Guideline quality was evaluated by a panel of multidisciplinary experts who assessed the evidence level, strength of recommendation given to each statement, and the declaration of potential conflicts of interest.

Guideline content was then compared with EAPC recommendation content in order to identify additional topics to address in the new guidelines.

Expert consensus development

In order to gain consensus on the contents of the first set of statements, a modified two-round Delphi method was applied.[10] An international expert group of 40 members was invited to participate. This group included the co-authors of EAPC recommendations published in 2001 and a number of stakeholders representing either professionals

TABLE I.—*Quality of international guidelines for the use of opioid analgesics in the treatment of cancer pain, retrieved by systematic search.*

	Multidisc. expert group	Evidence based	Conflict of interest declaration
Scientific societies			
European Association for Palliative Care (2001). Morphine and alternative opioids in cancer pain: the EAPC recommendations.	YES	YES	NO
American Society of Anaesthesiology (2006). Practice guidelines for cancer pain management: a report by the American Anaesthesiology task force on pain management, cancer pain section.	YES	YES	NO
Scottish Intercollegiate Guidelines Network (2008). Control of pain in patients with cancer.	YES	YES	NO
American Geriatrics Society (2002). The management of persistent pain in older persons.	YES	YES	YES
Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva (2003). Recommendations on the assessment and treatment of chronic cancer pain.	YES	YES	NO
Quality Improvement Scotland (2004). The management of pain in patients with cancer.	YES	YES	NO
European Society for Medical Oncology (2007). Minimum clinical recommendations for the management of cancer pain.	YES	NO	NO
American Pain Society (2005). Guideline for the management of cancer pain in adults and children.	YES	YES	YES
National Comprehensive Cancer Network (2008). Clinical Practice Guidelines in Oncology. Adult Cancer Pain.	YES	YES	YES
Governative institutions			
National Institutes of Health (2002). Symptom management in cancer: pain, depression and fatigue.	YES	YES	YES
Singapore Ministry of Health (2003). Cancer pain	YES	YES	YES
National Health and Medical Research Council - Australian Government (2006). Guidelines for a palliative approach in residental aged care.	YES	YES	NO
Other institutions			
Joint Commission on accreditation of Healthcare Organizations (2001). Pain current understanding of assessment, management and treatments.	YES	YES	YES
MD Anderson Cancer Center (2003). Cancer pain.	YES	NO	NO
Texas Cancer Council (2005). Guidelines for treatment of cancer pain.	YES	YES	NO

with specific documented expertise in opioid pharmacotherapy or those interacting with cancer patients, such as volunteers, patient representatives and general practitioners. Participants were asked to score each key point on an eleven-point numerical scale (0=no relevance, 10=high relevance) concerning its relevance for the new guidelines. An *ad hoc* questionnaire containing all the key points was sent by e-mail to the experts, and free text space was allocated to encourage comments.

The first round data were then analyzed. Those statements with an average relevance score ≤6 were eliminated, those with a score ≥8 were accepted, while the remaining statements (relevance scores between 6 and 8) were circulated again in a second round.

The questionnaire used in the second round contained the previous score given by that expert for each statement, as well as the average and distribution of scores given by the

Table II.— *Comparison among EAPC and other guidelines recommendations.*

Recommendation	EAPC	MdA	SIGN	NCCN	APS	SIAARTI
Morphine as first choice	X		X	X		X
Optimal route is by mouth	X		X			X
Dose titration with normal release morphine	X	X	X	X	X	X
If pain return the regular dose must be increased	X		X	X		X
Changes to the regular doses should not be made <48 h	X					X
Double dose at bedtime for pts on NR morphine	X					X
All MR formulations are effective	X					X
The preferred alternative route is subcutaneous	X		X			X
The potency ratio oral/sc Mo is 1:2-1:3	X	X	X	X		X
Preferred continuous parenteral administration is s.c. infusion	X		X			X
Intravenous infusion of Mo in particular pts	X					X
The potency ratio oral/i.v. Mo is 1:2-1:3	X	X				X
Buccal, sublingual, nebulized routes are not recommended	X					X
OFTC is effective for BTP	X	X		X		X
Adequate analgesia without excessive adverse events	X			X		X
Alternative opioid or change in the route for those who develop adverse events with Mo	X		X			X
Hydromorphone or oxycodone are effective alternatives to oral Mo	X		X	X		X
Methadone is an effective alternative to oral Mo, but its more complicated to use	X	X	X	X		X
Transdermal fentanyl is an effective alternative to oral Mo	X		X	X		X
Spinal administration should be considered in particular pts	X			X	X	X

EAPC: European Association for Palliative Care; MdA: Md Anderson, SIGN: Scottish Intercollegiate Guidelines Network; NCCN: National Comprehensive Cancer Network; APS: American Pain Society; SIAARTI: Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva; SMH: Singapore Ministry of Health; ESMO: European Society of Medical Oncology; NIH: National Institute of Health; JCAHO: Joint Commission on Accreditation of Healthcare Organizations; ASA: American Society of Anaesthesiology; AGS: American Geriatrics Society; NHS: Quality Improvement Scotland; TCC: Texas Cancer Council; NHA: National Health and Medical Research Council – Australian Government.

global sample so that each responder could evaluate his previous answer in relation to those of other experts. Responders were then asked to rate, once again, each statement using the information from the previous round as feedback.

The criteria for accepting/eliminating the key points in the second round were the same as those of the first one; in cases of key points with a score between 6 and 8, decisions about the statement were made by the local and steering group members at the end of the consultation period.

In addition to this expert consultation, the key points were discussed and presented at one specialist course,[11] one meeting of experts with the EAPC board of directors [12] and three international conferences.[13-15]

SMH	ESMO	NIH	JCAHO	ASA	AGS	NHS	TCC	NHA
X						X	X	X
X	X			X		X	X	
X					X	X		
X	X							
			X					
X			X				X	
			X					
X	X		X				X	
				X		X		X
X	X					X		X
	X		X	X	X		X	
X	X			X	X		X	
X	X		X	X	X			
X					X			

The key points were also published in the EPCRC website [9] and the EAPC website [5] to collect public opinions.

Development of the final list of topics for systematic reviews

The key points chosen through the Delphi process were then elaborated into a number of topics for the systematic reviews necessary to the development of the new guidelines.

Results

Fourteen guidelines [16-29] on cancer pain treatment published or updated after 2000 were found (Table I). The following guidelines were

TABLE III.—*Quality of international guidelines for the use of opioid analgesics in the treatment of cancer pain, retrieved by systematic search.*

Key points	Origin	Average relevance score		Finally selected
		First round	Second round	
1. Identify the opioid of first choice for moderate to severe cancer pain (opioid of choice)	EAPC	7.3	7.5	YES
2. Identify the optimal route of administration of opioid of choice	EAPC	8.7	_	YES
3. Clarify the optimal method of opioid dose titration at the beginning of therapy	EAPC	8.0	_	YES
4. Suggest when a regular dose of opioid should be increased	EAPC	8.0	_	YES
5. Identify the roles of short acting and long-acting opioid of choice (while taking into account the availability of such formulation) to suggest different titration schedules	EAPC	8.2	_	YES
6. Consider a specific dosing schedule at bedtime for patients receiving short acting opioid of choice	EAPC	5.4	_	NO
7. Clarify that available formulations of long-acting first choice (and other) opioid do not differ in term of efficacy	EAPC	7.8	7.5	YES
8. Identify the preferred alternative route/s of administration for patients who are unable to take oral opioids	EAPC	8.2	_	YES
9. Establish the average relative potency ratio/s of oral opioid of choice to the parenteral route of choice	EAPC	8.5	_	YES
10. Identify the optimal way to administrate continuous parenteral opioid of choice	EAPC	7.4	7.1	YES
11. Identify indications for an intravenous infusion	EAPC	6.9	5.8	NO
12. Establish the average relative potency ratio of oral to intravenous opioid of choice	EAPC	7.6	7.5	YES
13. Establish the role of repetitive subcutaneous injections	OTH_ GL	5.9	_	NO
14. Establish the role of repetitive intramuscular injections	OTH_ GL	3.8	_	NO
15. Identify the role of other alternative routes of opioid of choice administration	EAPC	7.5	8.42	YES
16. How should breakthrough pain be managed	OTH_ GL	8.7	_	YES
17. Identify the role of opioids in the treatment of breakthrough pain	EAPC	8.9	_	YES
18. Address the needs of patients who do not achieve adequate analgesia without excessive adverse effects with the use of opioid of choice considering the spinal administration of analgesic, alternative opioids and non-drug methods of pain control	EAPC	7.9	8.7	YES
19. Identify the role of hydromorphone	EAPC	7.1	6.7	YES
20. Identify the role of oxycodone	EAPC	7.4	7.5	YES

(Continued)

not considered because they were not available in an electronic format ("Palliative treatment of cancer" by Finnish Medical Society) or in English: Norwegian guidelines "Lindring av smerter hos kreftpasienter", CeVEAS, Italy "Morfina orale e altri oppioidi nel dolore oncologico", French guidelines "Fèdèration Nationale des centres de lutte contre le cancer, Standards, options et recommandation pour les traitments antalgiques médicamenteux des douleurs canceréuses par excès de nociception chez l'adulte, mise à jour", and German guidelines "Therapieempfehlung Tumorschmerzen der Arzneimittelkommission der Deutschen Ärzteschaft".

In the majority of the guidelines obtained, the strength of each recommendation was clearly declared, in some the strengths it was not immediately obvious,[18, 27] and in others [16, 22, 24] the recommendations were expressed as expert opinions.

The content of these national and international guidelines was compared with the 20 EAPC recommendations (Table II). Not all 20 recommendations were compared with each guideline, and in some cases, the strength given to the recommendation was different even in cases where the recommendation was the same. For example, in the cancer pain guidelines of the Singapore Ministry of Health, [21] the recommendation, "the opioid of first choice for moderate to severe pain is morphine," is equal to grade B, while the same recommendation in the EAPC document is C.

Table III.—*Quality of international guidelines for the use of opioid analgesics in the treatment of cancer pain, retrieved by systematic search (Continued).*

Key points	Origin	Average relevance score		Finally selected
		First round	Second round	
21. Identify the role of methadone	EAPC	8.2		YES
22. Identify the role of transdermal fentanyl	EAPC	7.6	7.57	YES
23. Identify the role of buprenorphine (sublingual and transdermal)	OTH_ GL	7.4	6.9	YES
24. Identify the role of spinal administration of opioid analgesics in combination with other drugs	EAPC	7.3	7.7	YES
25. Identify the role of adjuvants in combination with analgesics	OTH_ GL	7.3	7.9	YES
25a. antidepressants	OTH_ GL	7.2	7.9	YES
25b. anticonvulsants	OTH_ GL	7.2	7.7	YES
25c. gabapentin and pregabalin	OTH_ GL	7.0	7.5	YES
26. Identify the role of opioids for mild to moderate cancer pain as suggested by step II of WHO analgesic ladder	OTH_ GL	7.9	8.3	YES
27. Identify the role of NSAIDs	OTH_ GL	7.4	8.4	YES
28. Identify the equivalent potency ratio of oral morphine to transdermal fentanyl	OTH_ GL	7.4	7.8	YES
29. Suggest an evidence based equipotency table for opioid conversion and its use in equianalgesic dose calculation	EXP	8.4	_	YES
30. Identify how and when to start management to prevent and treat opioids side effects	OTH_ GL	9.2	_	YES
31. Identify the treatment of constipation related to opioids	EXP	8.7	_	YES
32. Identify the role of using more than one opioid in combination	OTH_ GL	6.8	6.7	YES
33. Identify the role of bisphosphonates in the management of cancer pain	EXP	5.5	-	NO
34. Identify the role of specific invasive procedures (coeliac plexus block, cordotomy, nerve block)	EXP	5.4	-	NO
35. Identify which opioids to use in renal failure	EXP	8.5	-	YES
36. Identify which opioids to use in liver failure	EXP	7.9	7.2	YES
37. Identify the role of antineoplastic treatment in combination with opioids in the control of pain	EXP	5.4	-	NO

EAPC: from EAPC recommendations; OTH-GL: from other guidelines; EXP: from experts contribution.

Many guidelines included additional subjects not covered by EAPC recommendations, *e.g.*, indications for the use of adjuvant drugs, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, radionuclides and radiotherapy. The comparison of these guidelines led to the formulation of 31 key points and the WP 3.1 local and steering group members suggested 6 further statements. A list of 37 key points (Table III) was submitted to the panel of experts for the first Delphi round.

Out of 40 international experts, 25 sent back a completed questionnaire (23 physicians with different specialties and two nurses). Six key points were eliminated (points 6, 13, 14, 33, 34, 37), 13 accepted (points 2, 3, 4, 5, 8, 9, 16, 17, 21, 29, 30, 31, 35) and 18 obtained a score between 6 and 8 (Table III) and so were submitted again to the panel for the second Delphi round.

Nineteen experts filled in the second questionnaire (average relevance scores are reported in Table III). As result of this second round, key point 11 was eliminated, key points 15, 18, 26, and 27 were accepted, but the remaining thirteen (points 1, 7, 10, 12, 19, 20, 22, 23, 24, 25, 28, 32, 36) still obtained an average score between 6 and 8, as experts often maintained their previous scores. The local and the steering group members decided to include all 13 statements. The possibility of a third Delphi round was also eliminated both because of the

TABLE IV.—*List of topics object of systematic literature reviews and corresponding key point.*

Topic	Key point
1. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that oral morphine is better than placebo, or other oral/ transdermal opioids in the management of pain?	1,2
2. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence of the best titration approach (a combination of initial dose, schedule for dose increase, choice between slow and immediate release formulation)?	3,4,5,7
3. In adult patients with moderate to severe pain directly due to cancer, and who are unable to take oral opioids, which is the evidence that one potential alternative route (transdermal, parenteral, rectal, subcutaneous, intravenous, oral transmucosal and nasal) is to be preferred over the others in the management of pain?	8,10,15
4. In adult patients with moderate to severe pain directly due to cancer and who do not experience a favourable balance between analgesia and side effects with the administration of one strong opioid, which is the evidence that by switching therapy from one opioid to another one it is possible to improve analgesia or reduce the side effects?	18,19,20 21 22 23
5. In adult patients with pain directly due to cancer, which is the evidence of the optimal equianalgesic ratios between different opioids and strategies for switching therapy from one opioid to another one?	9,12,28,29
6. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that oral hydromorphone is better than placebo, or other oral/transdermal opioids in the management of pain?	19
7. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that oral oxycodone is better than placebo, or other oral/transdermal opioids in the management of pain?	20
8. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that oral methadone is better than placebo, or other oral/transdermal opioids in the management of pain?	21
9. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that transdermal fentanyl is better than placebo, or other oral/transdermal opioids in the management of pain?	22
10. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that oral or transdermal buprenorphine is better than placebo, or other oral/transdermal opioids in the management of pain?	23
11. In adult patients with pain directly due to cancer, which is the evidence of the best opioid given by any route for breakthrough pain management?	16, 17
12. In adult patients with pain directly due to cancer, which is the evidence of the effectiveness and side effects of ketamine when added on opioid therapy with respect to opioid therapy alone or to opioid therapy plus another adjuvant?	25
13. In adult patients with pain directly due to cancer, which is the evidence of the effectiveness and side effects of adjuvant drugs (antidepressants, anticonvulsants, gabapentin, pregabalin) when added on opioid therapy with respect to opioid therapy alone or to opioid therapy plus another adjuvant?	25a,b,c
14. In adult patients with pain directly due to cancer, which is the evidence of the effectiveness and side effects of NSAIDs alone or combined with opioid therapy?	27
15. In adult patients with slight to moderate pain directly due to cancer and never treated with opioids, which is the evidence that codeine, tramadol and low dose oxycodone WHO step II drugs are better than placebo, or other opioids in the management of pain?	26
16. In adult patients with pain directly due to cancer and never treated with opioids, which is the evidence that it is better to use one step II opioid instead of a step III opioid?	26
17. In adult patients treated with opioid therapy for pain due to cancer, which are the evidences to support the best strategy in the management of opioids side effects (nausea and vomiting, constipation)?	30,31
18. In adult patients treated with opioid therapy for pain due to cancer, which are the evidences to support the best strategy in the management of opioids side effects (sedation, delirium/hallucination and myoclonus, other/s)?	30
19. In adult patients with pain directly due to cancer and liver failure, which is the evidence to support the safe use of opioids?	36
20. In adult patients with pain directly due to cancer and renal failure, which is the evidence to support the safe use of opioids?	35
21. In adult patients with pain directly due to cancer, which is the evidence that the balance between analgesia and side effects can be improved by combining two opioids in comparison with increasing the dose of one of them, or with other strategies?	32
22. In adult patients with pain directly due to cancer, which is the evidence to support the use of spinal opioids alone or in combination with other drugs in case of an unfavourable balance between analgesia and side effects?	24

potential for further reduction in the number of experts responding, which would lead to a low potency for each statement score, and because of the low propensity of the responders to change their previous scores as shown in the data from rounds 1 and 2. The final list of 30 key points (Table III) was then elaborated by the WP 3.1 local and steering committees to identify the objects of 22 systematic reviews (Table IV).

Discussion

The impact of guidelines is affected by several factors: the nature of the organization producing the guidelines, the content, the channels used for diffusion of information, and the characteristics of the intended users.

This work is oriented to perform a systematic review of the content to treat in the new guidelines. In the end, the aim is not only to update the EAPC recommendations but also to enforce them with new evidence and to disseminate the information as much as possible to maximize the intended benefits. In fact, a guideline can be perfectly "valid" from a scientific point of view, but still fail to be a true asset for the patients or the health care system.

In a recent survey conducted in Europe and Israel on patients with pain related to cancer, the findings indicated that cancer pain is far from optimally treated as a consistent number of patients do not receive any analgesic drugs for their pain. These results therefore disproved the notion that cancer pain is better managed than other types of chronic, non-malignant pain.[1]

It is likely that improvement in the management of cancer pain can be obtained with the development and circulation of specific, updated guidelines, endorsed by international bodies in order to influence national and local practices and regulations. Cancer pain management is at the core of the clinical mission and scientific attention to palliative care and palliative medicine. Furthermore, it can be viewed as an index symptom in highlighting the need for the adherence of palliative medicine to the requirements of modern health-care organizations which demand that health-care providers follow standard evidence-based clinical practices.[30, 31]

The assessment of guideline quality is based on a declaration of the strength of each recommendation, evidence provided, formal consensus processes (type of consensus used, appropriateness of expert recommendations), and transparency of preparation process steps.

The WHO guidelines on cancer pain relief published in 1986 had a very important role in cancer pain management, even if their impact was not well-demonstrated.[6] The EAPC recommendations have already emphasized the role of opioids, but with the increasing growth and international availability of these drugs these guidelines are outdated and need to be revised. The evidence base for cancer opioid guidelines in particular needs to be revised in light of the most recent literature developments.

Most of the available guidelines have overlapping content when compared to EAPC recommendations.

The comparison of different guidelines in Table II clearly shows significant variation in some very relevant topics, such as the role of morphine as a first-line drug, which deserve a revaluation of the available evidence and an application of an international process for more standardized treatments approaches. In some cases, the guidelines provide recommendations the same as or only partially modified those from the EAPC. Based on the comparison between EAPC recommendations and the other guidelines, our formal expert consensus confirmed the relevance of previously included topics and added a number of subjects. Very few guidelines give formal information about the process of their development and often they are based on precarious methodologies and on the context of development.

A two-round Delphi method was used to collect the consensus opinions of a panel of experts concerning topics to develop in the revised guidelines.[32, 33] The classical original Delphi is composed of four rounds, but in other formats, such as "policy Delphi", "real-time Delphi" and "modified Delphi", there can be two or three rounds. This is because it is difficult to obtain a high response rate using a method with

a large number of rounds. With each additional round, the response rate may decline, whereas a lower number of rounds ensures that people who have agreed to participate stay involved until the final round.

The process discussed in this study offers advantages over previous work of this kind due to the systematic review of available guidelines, which, to our knowledge, has not been performed before. An additional advantage of this method is the large European and international contributions to the project. Limitations which might influence the impact of the project include the declared focus on opioids, which can overshadow other treatment strategies. This leads to a lack of information in the final guidelines concerning integration of other methods, such as palliative tumor-directed interventions and supportive interventions like chemo- and radiotherapy, bisphosphonates and radionucleotides. However, it is true that while focusing on opioids, the guidelines will also include their relationship to other approaches (Table III); moreover, the proposed guidelines should be further developed in a dynamic process of revision which will allow for new developments and more comprehensive versions in future updates.

Conclusions

This article presents the process and methodology adopted to revise the present EAPC guidelines. Furthermore, it offers a review of the available international guidelines on cancer pain management. The final version of the "Evidence-based guidelines for the use of opioid analgesics in the treatment of cancer pain: the EAPC recommendations" will be based on the results of the 22 systematic literature reviews.

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