

Key concepts in palliative care: the IAHPC list of essential medicines in palliative care

Liliana De Lima

Background This paper describes the process of developing a list of essential medicines in palliative care based on a consensus of experts.

Method Phase I: guiding principles and identifying the most prevalent symptoms in palliative care. Phase II: identifying the medications used to treat the symptoms, developing an initial list of medicines with a survey of 40 physicians, and implementing a Delphi survey. 112 physicians and pharmacologists were invited to rate the safety and efficacy of each medication. Phase III: representatives of 28 pain and palliative care organisations were invited to a meeting. 26 accepted (93% RR). Participants were split into groups and received the results of the Delphi survey. Groups were instructed to base the discussions on medications for which at least 50% of the respondents rated both safe and effective (score of 7 or above).

Results 21 symptoms were identified as the most common in palliative care. 120 medications were recommended to treat these symptoms. 71 participants (63% RR) responded to the Delphi survey. A final list with 33 medications was approved as the International Association for Hospice and Palliative Care (IAHPC) essential medicines list for palliative care. There was no consensus among respondents in recommending medications as safe and effective for bone pain, dry mouth, sweating, fatigue or hiccups.

Conclusion Additional research is needed to identify safe and effective medications to treat these symptoms. The IAHPC will soon be implementing a project to update the list of essential medicines in palliative care to reflect these new findings.

Introduction

According to the WHO, essential medicines are those that satisfy the primary healthcare needs of the population.¹ The concept was laid down by the WHO in 1977 with the recommendation that essential medicines be selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and at a price the individual and the community can afford.

To advance application of the concept, the WHO has also developed a model list of essential medicines which is updated every 2 years. The concept and the model list are presented to countries as expert guidelines which they can use to develop

their own essential medicines policies and lists.

Scope of the problem

According to data from the WHO, in spite of recent progress, a large part of the world's population still has little or no access to essential medicines. This results in enormous unnecessary suffering and loss of life, particularly among the poor, and massive damage to national economies.²

A significant problem is the lack of access to pain relief. Morphine (immediate and sustained release oral and injectable) is included in the current WHO model list in the analgesics section.³ However, several reports from the United Nations, the WHO, the International Narcotics Control Board and other organisations have indicated that opioid analgesics are insufficiently available, particularly in developing countries.⁴⁻⁷ In many countries, opioid use is prohibited or restricted by national laws and access is limited by extreme costs, regardless of the patients' needs.^{8,9} Recently, many organisations, individuals, academic centres, advocacy groups and pain and palliative care

organisations have been working towards improving access to all medications needed to treat the most common symptoms in palliative care, not just pain.^{10,11}

Process and results

The concept of essential medicines can also be applied to palliative care, and under this framework the WHO Cancer Control Programme requested support from the International Association for Hospice and Palliative Care (IAHPC) to develop a list of essential medicines for palliative care. In response, the IAHPC formed a working group (WG) which included board members of the IAHPC and external advisors. The WG developed a plan of action and a list of essential medicines in palliative care ('list') by following these steps.

Guiding principles

The following set of principles were identified and adopted to guide the process:

- ▶ The list was developed by palliative care workers from around the world with a commitment to provide palliative care to

Correspondence to Dr L De Lima, International Association for Hospice and Palliative Care (IAHPC), 5535 Memorial Dr Suite F—PMB 509, Houston, Texas 77007, USA; ldelima@iahpc.com

patients in need, regardless of condition, race, religion, diagnosis or location.

- ▶ The list is not a directive but offered as guidance to be adopted by each group or institution depending on the socioeconomic conditions and the needs of its patients.
- ▶ The list was developed with the aim of facilitating provision of the best possible care for all those with advanced life threatening illness.
- ▶ The list has to be appropriately disseminated, advocated for and incorporated into the curricula to result in any significant benefit to patients.
- ▶ The list is not an endorsement of any product, does not assume similar pharmacological action or adverse effects among medications within the same class, and should not be read as promoting a proprietary preparation.
- ▶ The list should be reviewed and updated periodically, taking into account research findings, changes in practice and constructive comments from palliative care workers worldwide.

Identifying the most prevalent symptoms in palliative care

After several discussions among the committee members, it was agreed that the best approach was to start with a list of the most common symptoms in palliative care. It was also agreed that the group would focus on symptoms and not the treatment of underlying conditions; therefore, the treatment of diseases such as cancer, HIV and other infections were excluded. Based on a literature review, an initial list of the 21 most common symptoms in palliative care was developed by the WG. Table 1 includes the most common symptoms in palliative care.

Identifying the medications used to treat these symptoms

IAHPC board members and other palliative care leaders from around the world were asked to propose appropriate medications for these symptoms identified above (the most common symptoms in palliative care). Of a total of 40, 34 physicians responded (85%), 15 from developing countries. In total, they recommended 147 products. This initial list was decreased to 120 by removing non-medications (ie, oxygen and vitamins) and duplicates.

Online survey and Delphi process

An online Delphi survey¹² of 19 rating panels (one for each symptom and four for pain: mild to moderate; moderate to severe; visceral pain and bone pain)

was sent by email to 112 physicians and pharmacologists (77 from developing countries). Using a scale of 1–9, participants were asked to rate the safety and efficacy of each medication. Ratings were done separately, using the following guidelines: ratings of 1–3 meant that the drug class or medication was not safe or effective for treating that specific symptom in palliative care populations; ratings of 4–6 meant that there was considerable variability in the safety and effectiveness of that drug class or medication for treating that specific symptom in palliative care populations; and ratings of 7–9 meant that drug class or medication was very safe and effective for treating that specific symptom.

Seventy-one participants (63%) responded to the Delphi survey. Results from the survey indicated there was little consensus among the respondents to recommend medications as both safe and effective for five of the 23 symptoms: bone pain, dry mouth, fatigue, hiccups and sweating.

Final list

Twenty-eight global, regional and professional organisations working in pain and palliative care were invited to a meeting in Salzburg, Austria, on 30 April to 2 May 2006. Thirty-one representatives from 26 of these organisations attended.

Participants received a copy of the current WHO model list of essential medicines and the results of the Delphi survey, and were divided into three WGs. Each group considered medications for a specific set of symptoms:

- ▶ Medications used to treat mental health symptoms
- ▶ Medications to treat pain
- ▶ Medications to treat gastrointestinal symptoms

A few 'orphan' symptoms (eg, hiccups) were randomly assigned to each group. Led by a skilled moderator, each group held a structured discussion addressing agreement and disagreement about medications under consideration as 'essential medications' for each symptom. Groups were instructed to base the discussions particularly on those medications for which at least 50% of the respondents rated as both safe and effective (score of 7 or above). For several groups of medications, in which the Delphi survey did not result in the 50% consensus described above, the group was asked to review the comprehensive list and make recommendations based on their expertise.

Using the results from the Delphi survey and by a process of coming to consensus, each group identified the

Table 1 Most common symptoms in palliative care

Pain	
Mild to moderate	
Moderate to severe	
Bone*	
Neuropathic	
Visceral	
Dyspnoea	Fatigue*
Terminal respiratory congestion	Anxiety
Dry mouth*	Depression
Hiccups*	Delirium
Anorexia-cachexia	Insomnia
Constipation	Terminal restlessness
Diarrhoea	Sweating*
Nausea	
Vomiting	

* The expert group determined after the process was completed that there was not enough evidence to recommend any medications as both safe and effective for these five symptoms.

medications they considered essential for each symptom. The chairs of each group then shared the results with all participants and a general discussion ensued. When there were differences of opinion, alternatives were discussed and the best option was decided by consensus. Thus each of the medications included in the IAHPC list was reviewed and approved by the conference participants as a whole.

The final list of medications was approved by the participants as the IAHPC Essential Medicines List for Palliative Care. The IAHPC list includes 33 medications of which 14 are already included in the WHO list as essential in the treatment of several conditions, some of which are common in palliative care. The inclusion of a medication in one section of the WHO list does not preclude its inclusion in a different section, if the medication is determined by WHO to be essential for the treatment of different conditions. The list can be downloaded freely from the IAHPC website (www.hospicecare.com).

The group agreed with the respondents of the survey in that there is not enough evidence to recommend any medications as both safe and effective for five of the symptoms: bone pain, dry mouth, sweating, fatigue and hiccups, and recognised that additional research is needed to identify safe and effective medications to treat these symptoms.

IAHPC informed the medical and palliative care communities about the list and the consensus process by sending reports, press releases and by publishing articles and announcements in peer reviewed journals.^{13–16}

Limitations

This project focused mostly on medications to treat major symptoms of advanced cancer, recognising that the agents

Table 2 IAHP List of Essential Medicines in Palliative Care

Medication	Formulation	Indication for Palliative Care
Amitriptyline*	50-150 mg tablets	Depression Neuropathic pain Constipation
Bisacodyl	10 mg tablets 10 mg rectal suppositories	Neuropathic pain Depression
Carbamazepine**	100-200 mg tablet	Neuropathic pain
Citalopram (or any other equivalent generic SSRI except paroxetine and fluvoxamine)	20 mg tablets 10 mg/5ml oral solution	Depression
Codeine	20-40 mg injectable 30 mg tablets	Diarrhea Pain - mild to moderate Anorexia Nausea Neuropathic pain Vomiting Anxiety
Dexamethasone	0.5-4 mg tablets 4 mg/ml injectable	Diarrhea Pain - mild to moderate Anorexia Nausea Neuropathic pain Vomiting Anxiety
Diazepam	2.5-10 mg tablets 5 mg/ml injectable	Diarrhea Pain - mild to moderate Anorexia Nausea Neuropathic pain Vomiting Anxiety
Diclofenac	10 mg rectal suppository 25-50 mg tablets	Pain - mild to moderate
Diphenhydramine	50 and 75 mg/3ml injectable 25 mg tablets	Nausea Vomiting Pain - moderate to severe
Fentanyl (transdermal patch)	50 micrograms/hr tablets 300 mg or 400 mg	Neuropathic pain Delirium Nausea Vomiting Terminal restlessness Nausea Terminal respiratory congestion Visceral pain Vomiting Pain - mild to moderate
Gabapentin	0.5 - 5 mg tablets	Neuropathic pain Delirium Nausea Vomiting Terminal restlessness Nausea Terminal respiratory congestion Visceral pain Vomiting Pain - mild to moderate
Haloperidol	0.5 - 5 mg drops 0.5 - 5 mg/ml injectable	Neuropathic pain Delirium Nausea Vomiting Terminal restlessness Nausea Terminal respiratory congestion Visceral pain Vomiting Pain - mild to moderate
Hyoscine butylbromide	20 mg/1ml oral solution 10 mg tablets 10 mg/ml injectable	Neuropathic pain Delirium Nausea Vomiting Terminal restlessness Nausea Terminal respiratory congestion Visceral pain Vomiting Pain - mild to moderate
Ibuprofen	200 mg tablets 400 mg tablets	Delirium Terminal restlessness Diarrhea Anxiety Insomnia
Levomopromazine	5 - 50 mg tablets 25 mg/ml injectable	Delirium Terminal restlessness Diarrhea Anxiety Insomnia
Loperamide	2 mg tablets	Diarrhea Anxiety Insomnia
Lorazepam***	0.5-2 mg tablets 2 mg/ml liquid/drops	Diarrhea Anxiety Insomnia
Megestrol Acetate	2-4mg/ml injectable 160 mg tablets 40 mg/ml solution	Anorexia
Methadone (immediate release)	5mg tablets	Pain - moderate to severe
Metoclopramide	1 mg/ml oral solution 10 mg tablets	Nausea Vomiting Anxiety Terminal restlessness
Midazolam	5 mg/ml injectable 1-5 mg/ml injectable	Nausea Vomiting Anxiety Terminal restlessness
Mineral oil enema		
Mirtazapine (or any other generic dual action NassA or SNRI)	15-30 mg tablets	Depression
Morphine	7.5-15 mg injectable Immediate release: 10-60 mg tablets Immediate release: 10mg/5ml oral solution Immediate release: 10 mg/ml injectable Sustained release: 10 mg tablets Sustained release: 30 mg tablets	Dyspnea Pain - moderate to severe
Octreotide	100 mcg/ml injectable	Diarrhea Vomiting Diarrhea Pain - moderate to severe Pain - mild to moderate
Oral rehydration salts		
Oxycodone	5 mg tablet	Pain - moderate to severe
Paracetamol (Acetaminophen)	100-500 mg tablets 500 mg rectal suppositories 5 mg tablet	Pain - mild to moderate
Prednisolone (as an alternative to Dexamethasone)		Anorexia
Senna	8.6 mg tablets	Constipation
Tramadol	50 mg immediate release tablets/capsules 100mg/1ml oral solution 50mg/ml injectable	Pain - mild to moderate
Trazodone	25-75 mg tablets	Insomnia
Zolpidem (still patented)	50 mg injectable 5-10 mg tablets	Insomnia

Complementary: Require special training and/or delivery method

* Side-effects limit dose

** Alternatives to amitriptyline and tricyclic antidepressants (should have at least one drug other than dexamethasone)

*** For short term use in insomnia

Notes:

Non Benzodiazepines should be used in the elderly

Non Steroidal Anti Inflammatory Medicines (NSAIDs) should be used for brief periods of time

NO GOVERNMENT SHOULD APPROVE MODIFIED RELEASE MORPHINE, FENTANYL OR OXYCODONE WITHOUT ALSO GUARANTEEING WIDELY AVAILABLE NORMAL RELEASE ORAL MORPHINE.

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Key messages

The IAHPCL List of Essential Medicines:

- ▶ Includes 33 medications for the treatment of the most common symptoms in palliative care.
- ▶ Was developed through a consensus process of palliative care providers and representatives of pain and palliative care organisations from around the world.
- ▶ Serves as a reference to care providers and institutions around the world as a model list.
- ▶ Is available in English, French and Spanish.

considered are also essential for the treatment of similar symptoms in patients with other disorders. Nevertheless, it will need to be reconsidered to address specific features of other disorders and other symptoms in the future.

The project did not address cost and affordability issues as these were to be addressed in different settings and with other participants.

The list was developed for adult patients—a list for children with palliative care needs is urgent and should be developed. An expert panel convened by WHO put together a recommended list for paediatric palliative care in 2008.¹⁷ Additional research to evaluate the safety and efficacy of these medications needs to be carried out.

Future

The IAHPCL obtained the copyright to the List of Essential Medicines for Palliative Care and has granted permission to all those interested to reproduce and use the list as an advocacy tool to promote access to palliative care. It especially encouraged the use of the list as a model for countries in which there currently is limited availability and problems in accessing opioid analgesics and other palliative medications and for the development of national palliative medication lists tailored to local needs and resources.

The IAHPCL List of Essential Medicines in Palliative Care was developed more than 5

years ago. Since then, additional studies have been conducted on the efficacy and safety of several medications, including some included in the IAHPCL list. The IAHPCL will soon be implementing a project to update the list of essential medicines in palliative care to reflect these new findings.

Conclusion

The majority of the medications included in the IAHPCL list are simple and inexpensive while a few require special training or delivery methods. In compiling the list, the group was able to learn how very often simpler, less complicated, less expensive medications can be equally effective in the management of symptoms. In the process of selecting the medications, the group was careful in recommending those for which sufficient experience and information is available to ensure both their efficacy and safety.

The IAHPCL expects the updated version of the list to maintain the same principles.

Acknowledgements The author and the IAHPCL are grateful to the individuals who responded to the surveys and the representatives of the palliative care organisations in the meeting. Due to the long list of participants, it is not possible to print all of their names. However, the authors acknowledge their valuable contribution; the IAHPCL List of Essential Medicines in Palliative Care is based on their responses and suggestions. Kathy Foley, Neil Mac Donald, Eduardo Bruera, David Currow and LDL conceived and designed the original proposal. Peter Glassman and Karl Lorenz served as external advisors.

Competing interests None.

Contributors LDL was involved in the study design, data analysis and interpretation, and developed the manuscript. LDL is the guarantor.

Data sharing statement Additional datasets (STROBE checklist) with the raw data resulting from the surveys in this study are available with no restrictions and in pdf format from the author (ldelima@iahpc.com).

Provenance and peer review Commissioned; not externally peer reviewed.

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