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Special Report

The International Association for Hospice and Palliative Care List of Essential Medicines for Palliative Care*

Liliana de Lima on behalf of the IAHPC

Background

The World Health Organization (WHO) Cancer Control Program requested the support from the International Association for Hospice and Palliative Care (IAHPC) to develop a definitive list of essential medicines for palliative care.

The current WHO Model List of Essential Medicines has a section headed Palliative Care, which does not list any medications, but includes the following statement:

The WHO Expert Committee on the Selection and Use of Essential Medicines recommended that all the drugs mentioned in the WHO publication Cancer Pain Relief: with a Guide to Opioid Availability, second edition, be considered essential. The drugs are included in the relevant sections of the Model List, according to their therapeutic use, e.g. analgesics.

The request from WHO was to prepare a list based on recommendations from palliative care experts, taking into consideration two criteria: efficacy and safety. The WHO will be carrying out the cost effectiveness analyses and evidence-based reviews of the recommended medications.

To work on this proposal, IAHPC formed a working committee chaired by Dr Neil MacDonald (Canada) and co-chaired by Dr Carla Ripamonti (Italy). Other members included Dr Kathy Foley (USA), Dr Eduardo Bruera (USA), Dr David Currow (Australia) and Ms Liliana De Lima (USA). Dr Peter Glassman (USA) and Dr Karl Lorenz (USA) served as expert advisors. The Committee developed a plan of action, which included the following steps.

1. Identifying the most prevalent symptoms in palliative care

After several discussions among the committee members, it was agreed that the best approach to build a list of essential drugs 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.

An initial list of the 21 most common symptoms in palliative care was developed (Table 1).

2. First list: 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 the symptoms identified in step one.

Of a total of 40, 34 physicians responded (85%), 15 from developing countries. In total they recommended 147 products. This initial list was reduced to 120 by removing non-medications (i.e. oxygen and vitamins) and duplicates.

Table 1 Most common symptoms in palliative care

Pain:	Constipation
Mild to moderate	Diarrhea
Moderate to severe	Nausea
Bone	Vomiting
Neuropathic	Fatigue
Viscera	Anxiety
Dyspnea	Depression
Terminal respiratory congestion	Delirium
Dry mouth	Insomnia
Hiccups	Terminal restlessness
Anorexia–cachexia	Sweating

*see also this issues Editorial.

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3. Second list: online survey and modified Delphi process

An online survey 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 and were given the following definitions.

i) **Effectiveness:** a drug class or medication is defined as effective for treating a specific symptom in a palliative care population based on consideration of:

Evidence of treatment effectiveness: The strongest evidence is derived from randomized controlled trials (RCTs), but other experimental designs, observational studies, and expert opinion are also useful in rating this issue in the absence of RCTs. With respect to drug class, the evidence should be consistent across drugs within a group.

Ratings of 1–3 mean that the drug class or medication is not effective for treating that specific symptom in palliative care populations; ratings of 4–6 mean that there will be considerable variability in the effectiveness of that drug class or medication for treating that specific symptom in palliative care populations; and ratings of 7–9 mean that drug class or medication is very effective for treating that specific symptom.

ii) **Safety:** the safety profile of an agent, when used in a clinically appropriate manner, is sufficiently known (and/or described) in the target and/or general population so that adverse events can be anticipated and, if possible, prevented; or, when they occur, can be duly recognized and mitigated. In addition, the safety profile of one agent should be viewed in context of its pertinent comparators.

Ratings of 1–3 mean that drug class or medication is not safe for use in palliative care populations; ratings of 4–6 mean that there will be considerable variability in the safety of using a drug class or medication in palliative care populations; and ratings of 7–9 mean that the drug class or medication is very safe to use in this population.

Seventy one participants (63%) responded to the modified Delphi survey. Results from the modified Delphi

Table 2 Organizations represented in the Salzburg Meeting

Name	Representing	Country
Vanessa Adams	Velindre NHS Trust and Hospice Africa, Uganda	UK and Uganda
Carla Alexander	National Association for Palliative Care (NHPCO)	USA
Matti Aapro	Multinational Ass. For Supportive Care in Cancer (MASCC)	Switzerland
Mary Callaway	International Palliative Care Initiative Open Society Institute	USA
Jim Cleary	American Academy of Hospice and Palliative Medicine (AAHPM)	USA
Paul Daeninck	Canadian Society of Palliative Care Physicians	Canada
Franco De Conno	European Association for Palliative Care (EAPC)	Italy
Derek Doyle	National Council for Palliative Care	UK
Marilene Filbert	European Association for Palliative Care (EAPC)	France
Kathy Foley	International Palliative Care Initiative-Open Society Institute	USA
Reena George	Christian Medical College, Vellore	India
Peter Glassman	USA Veterans' Administration Medical Center	USA
Cynthia Goh	Asia Pacific Hospice Palliative Care Association (APHN)	Singapore
Luigi Grassi	International Psycho Oncology Society (IPOS) and World Psychiatric Association	Italy
Elizabeth Gwyther	Hospice and Palliative Care Association of South Africa (HPCA)	South Africa
Geoffrey Hanks	International Association for the Study of Pain (IASP)	UK
Eric Krakauer *(rapporteur)*	Vietnam CDC, Harvard Medical School AIDS Partnership (VCHAP)	USA
Freida Law	Li Ka Shing Foundation	China
Jacek Luczak	Eastern and Central Europe Palliative Care Task Force	Poland
Anne Merriman	African Palliative Care Association	Uganda
David Praill	Help The Hospices	UK
Debra Rowett	Palliative Care Australia	Australia
Maryna Rubach	European Society of Medical Oncology	Poland
Erdine Serdar	European Federation of IASP Chapters (EAFIC)	Turkey
Robert Wenk	Latin America Association for Palliative Care (ALCP)	Argentina
IAHPC		
Neil MacDonald *(Chair)*	International Association for Hospice & Palliative Care (IAHPC)	Canada
Carla Ripamonti *(Co-Chair)*	International Association for Hospice & Palliative Care (IAHPC)	Italy
Liliana DeLima *(Coordinator)*	International Association for Hospice & Palliative Care (IAHPC)	USA
WHO (as observers)		
Suzanne Hill	WHO Department of Medicines Policy and Standards	Switzerland
Willem Scholten	WHO Department of Medicines Policy and Standards	Switzerland
Cecilia Sepulveda	WHO Cancer Control Program	Switzerland

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.

4. Final list

Twenty eight global, regional and professional organizations working in pain and palliative care were invited to a meeting in Salzburg, Austria on April 30–May 2, 2006. Thirty one representatives from 26 of these organizations attended. Table 2 includes the list of participants and organizations represented in the meeting. This meeting was co-funded and hosted by the Palliative Care Initiative of the Open Society Institute (OSI).

Some presentations were given to the group, about the WHO Model List, the use and access to controlled substances, the process of selecting a formulary for the Veteran's Administration Hospitals in the USA and the process of developing a model list for palliative care in Australia.

A set of principles to guide the discussions and the meeting were also presented and are reproduced in the editorial of this issue of *Palliative Medicine*.

Participants were split among three working groups. Each was assigned a chair to lead the discussions. The groups and their corresponding chairs were:

Luigi Grassi, Medications used to treat mental health symptoms
Franco De Conno, Medications to treat pain
James Cleary, Medications to treat gastrointestinal symptoms

A few 'orphan' symptoms (i.e. hiccups) were randomly assigned to each group.

Each sub-group proceeded to discuss and select among the medications with the highest ratings in the Delphi survey, those they considered essential for each symptom.

The combined group reviewed and discussed the list proposed by each sub-group. When there were differences in the opinions of the participants, the group discussed the alternatives and the best option was decided by consensus. Through this process, each one of the recommended medications was reviewed and if agreed among the whole group, it was included in the IAHPC list.

The final list of medications was approved by the participants as the IAHPC Essential Medicines List for Palliative Care which is included below. The third column describes the IAHPC indication for palliative care and the fourth column identifies those medications which are already included in the WHO Model List of Essential Medicines as well as the treatment indications by WHO.

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 recognized that additional research is needed to identify safe and effective medications to treat these symptoms.

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.

5. The future

IAHPC encourages countries to use this list as a model and develop their own list of medications for palliative care, tailored to meet the needs of their patients and taking into account their own resources and medications available.

IAHPC encourages additional debate and discussion to move this list forward, improve it and find ways to improve the access to medications.

The IAHPC list of essential medicines for palliative care

Medication	Formulation	IAHPC indication for PC	WHO Essential Medicines Model List section, subsection and indication
*Amitriptyline**	50–150 mg tablets	Depression Neuropathic pain	24.2.1 – Depressive dissorders
Bisacodyl	10 mg tablets 10 mg rectal suppositories	Constipation	Not included
Carbamazepine**	100–200 mg tablet	Neuropathic pain	5 – Anticonvulsants/antiepileptics 24.2.2 – Bipolar disorders
Citalopram (*or any other equivalent generic SSRI except paroxetine and fluvoxamine)*	20 mg tablets 10 mg/5 ml oral solution 20–40 mg injectable	Depression	Not included
Codeine	30 mg tablets	Diarrhea Pain – mild to moderate	2.2 – Opioid analgesics 17.5.3 – Antidiarrheal
Dexamethasone	0.5–4 mg tablets 4 mg/ml injectable	Anorexia Nausea Neuropathic pain Vomiting	3 – Antiallergics and anaphylaxis 8.3 – Hormones and antihormones
Diazepam	2.5–10 mg tablets 5 mg/ml injectable 10 mg rectal suppository	Anxiety	1.3 – Preoperative sedation short term procedures 5 – Anticonvulsants/antiepileptics 24.3 – Generalized anxiety, sleep disorders
Diclofenac	25–50 mg tablets 50 and 75 mg/3 ml injectable	Pain – mild to moderate	Not included
Diphenhydramine	25 mg tablets 50 mg/ml injectable	Nausea Vomiting	Not included
Fentanyl (transdermal patch)	25 micrograms/hr 50 micrograms/hr	Pain – moderate to severe	Not included
Gabapentin	tablets 300 mg or 400 mg	Neuropathic pain	Not included
Haloperidol	0.5–5 mg tablets 0.5–5 mg drops 0.5–5 mg/ml injectable	Delirium Nausea Vomiting Terminal restlessness	24.1 – Psychotic dissorders
Hyoscine butylbromide	20 mg/1 ml oral solution 10 mg tablets 10 mg/ml injectable	Nausea Terminal respiratory congestion Visceral pain Vomiting	Not included
Ibuprofen	200 mg tablets 400 mg tablets	Pain – mild to moderate	2.1 – Non opioids and NSAIMs
Levomepromazine	5–50 mg tablets 25 mg/ml injectable	Delirium Terminal restlessness	Not included
Loperamide	2 mg tablets	Diarrhea	Not included
Lorazepam***	0.5–1–2 mg tablets 2 mg/ml liquid/drops 2–4/ml injectable	Anxiety Insomnia	Not included
Megestrol Acetate	160 mg tablets 40 mg/ml solution	Anorexia	Not included

Methadone (immediate release)	5 mg tablets 1 mg/ml oral solution	Pain – moderate to severe	24.5 – Substance dependence
Metoclopramide	10 mg tablets 5 mg/ml injectable	Nausea Vomiting	17.2 – Antiemetics
Midazolam	1–5 mg/ml injectable	Anxiety Terminal restlessness	Not included
Mineral oil enema			Not included
Mirtazapine *(or any other generic dual action NassA or SNRI)*	15–30 mg tablets 7.5–15 mg injectable	Depression	Not included
Morphine	Immediate release: 10–60 mg tablets Immediate release: 10 mg/5 ml oral solution Immediate release: 10 mg/ml injectable Sustained release: 10 mg tablets Sustained release: 30 mg tablets	Dyspnea Pain – moderate to severe	2.2 – Opioid analgesics **Note:** Only immediate release is included in the WHO Model List. Sustained release morphine is not.
Octreotide	100 mcg/ml injectable	Diarrhea Vomiting	Not included
Oral rehydration salts		Diarrhea	17.5.1 – Oral rehydration
Oxycodone	5 mg tablet	Pain – moderate to severe	Not included
Paracetamol (Acetaminophen)	100–500 mg tablets 500 mg rectal suppositories	Pain – mild to moderate	2.1 – Non opioids and NSAIMs
Prednisolone (as an alternative to Dexamethasone)	5 mg tablet	Anorexia	3 – Antiallergics and anaphylaxis 8.3 – Hormones and antihormones 21.2 – Anti inflamatory agents
Senna	8.6 mg tablets	Constipation	17.4 – Laxatives
Tramadol	50–100 mg immediate release tablets 10 mg/5 ml oral solution 50 mg/ml injectable	Pain – mild to moderate	Not included
Trazodone	25–75 mg tablets 50 mg injectable	Insomnia	Not included
Zolpidem (still patented)	5–10 mg tablets	Insomnia	Not included

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 Inflamatory Medicines (NSAIMs) 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.