What are the essential medications in palliative care?

A survey of Australian palliative care doctors

Phillip D Good
MBBS, FRACP, is Staff Specialist, Newcastle Mater Misericordiae Hospital, New South Wales. phillip.good@mater.health.nsw.gov.au

John D Cavenagh
MBBS, FAChPM, is Senior Staff Specialist, Newcastle Mater Misericordiae Hospital, New South Wales.

David C Currow
BMed, MPH, FRACP, is Professor of Palliative and Supportive Services, Flinders University, South Australia.

David A Woods
MBBS, FACRRM, FAChPM, is Medical Specialist, Tasmanian Palliative Care Service (North), Tasmania.

Penelope H Tuffin
BPharm, PGDip, HospPharm, is a clinical pharmacist, Cancer Council of WA Cottage Hospice, Western Australia.

Peter J Ravenscroft
MBBS, FRACP, MD, FFPMANZCA, FAChPM, is Professor of Palliative Care, University of Newcastle, New South Wales.

BACKGROUND
There is a disparity of availability and cost of drugs in the community for palliative care patients through the Pharmaceutical Benefits Scheme (PBS) compared to those available to inpatients in public hospitals.

METHODS
The Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia surveyed palliative care practitioners in Australia to compile a list of drugs they considered essential.

RESULTS
Drugs nominated generally had good levels of evidence for use in palliative care, although many practitioners still used some without evidence of benefit.

DISCUSSION
We are now working with the Commonwealth Department of Health and Ageing to agree on a list of drugs for specific palliative care indications. As a result, the first ever section in the PBS for a specific patient population has been created. There is a need for high quality studies in palliative care to determine the best drugs to add to the list.

Many palliative care doctors feel that patients receiving palliative care in the community are disadvantaged in accessing drugs because the Pharmaceutical Benefits Scheme (PBS) constrains them. Members of the Australian and New Zealand Society for Palliative Medicine (ANZSPM) started to advocate to redress this. Barriers to changing the PBS regulations were: some drugs on the list require Therapeutics Goods Administration approval for palliative care indications; others needed evidence of effectiveness, cost effectiveness and clinical place in therapy for PBS listing; and these drugs would require an industry sponsor to fund and take on responsibility for the application and subsequent use, as required by Australian law – a problem as many drugs were out of patent.

As a way forward, a Joint Therapeutics Committee of Palliative Care Australia, ANZSPM, and the Clinical Oncological Society of Australia formed to generate a list of essential drugs for palliative care. One had previously been generated from a world survey sent to 50 palliative care doctors in 25 different countries (including Australia), and a list of what was thought the '20 essential drugs in palliative care' published.[1]

We decided to survey palliative care doctors in Australia to compile a similar list of essential drugs, and also to assess the level of evidence for them, setting out which were available through the PBS.

Method

We surveyed members of ANZSPM, asking them what they thought were essential drugs for palliative care. The questionnaire used a list of the 22 most frequently encountered symptoms derived from the literature, 'pain' occupying three of these. Respondents could list up to five individual drugs for each symptom, together with their estimated level of evidence for the drug for that indication, using a ranking of the evidence (*Table 1*). This differs from

Table 1. Levels of evidence used in the questionnaire

Level 1	Evidence from systematic review of all relevant randomised controlled trials
Level 2	Evidence from at least one properly designed randomised controlled trial
Level 3	Evidence from nonrandomised controlled trials, cohort studies, case control studies
Level 4	Evidence from case reports/expert opinion
Level 5	Unknown to respondent what level of evidence exists

current National Health and Medical Research Council (NHMRC) guidelines[2] in retaining the expert opinion no longer included in NHMRC guidelines. While these levels have been used throughout the article for consistency, where the only evidence available is expert opinion, that is denoted '4E'.

The questionnaire was hand delivered to registrants at a biennial scientific committee of ANZSPM held in Geelong (Victoria) in September 2000 and in addition, mailed to all other members not present.

The Hunter Area Research Ethics Committee gave ethics approval for this study.

Results

Out of 350 questionnaires, 102 were returned. Two were excluded because the address was unknown, giving a response rate of 100/350 (29%). Median age was 46 years (range 28–70), and median time since graduation was 21 years (range 5–49). Most respondent's (58%) main area of practice was palliative medicine, while the rest were mostly general practitioners with experience in palliative care.

The first ranked drug for selected symptoms, PBS availability, and level of evidence at the

Table 2. Palliative symptoms, with the drug nominated as 'essential' for that symptom, by symptom control, PBS subsidy, and perceived and actual evidence of benefit

Palliative symptom	Drug	% of respondents nominating this drug as first rank	PBS subsidy at time of survey (September 2000)	Level of evidence nominated by respondents	% responding	Level of evidence	Reference
Pain using opioid analgesics	Morphine	98	Yes	1 2 3 4 5	43 12 9 9 27	2	4
Pain using nonopioid analgesics	Paracetamol	88	Yes	1 2 3 4 5	43 5 11 9 32	1	5
Pain using adjuvant analgesics	Valproate	61	Yes	1 2 3 4 5	8 18 22 12 40	1	6
Dyspnoea	Morphine	94	No	1 2 3 4 5	9 18 26 15 31	2	7
End stage respiratory reflexes (grunting, secretions)	Hyoscine Hydrobromide	86	No	1 2 3 4 5	4 6 22 31 37	4	8
Terminal restlessness	Midazolam	81	No	1 2 3 4 5	5 8 15 31 41	4	9
Anorexia	Dexamethasone	69	Yes	1 2 3 4 5	6 20 20 19 35	2	10
Nausea	Metoclopramide	86	Yes	1 2 3 4 5	19 14 12 11 45	3	11

Table 2. (continued) Palliative symptoms, with the drug nominated as 'essential' for that symptom, by symptom control, PBS subsidy, and perceived and actual evidence of benefit

Palliative symptom	Drug	% of respondents nominating this drug as first rank	PBS subsidy at time of survey (September 2000)	Level of evidence nominated by respondents	% responding	Level of evidence	Reference
Constipation	Docusate and senna	58	No	1 2 3 4 5	9 12 14 17 48	4E	12
Dry mouth	Artificial saliva	39	No	1 2 3 4 5	– 9 15 6 70	2	13
Delirium	Haloperidol	84	Yes	1 2 3 4 5	21 16 13 11 39	2	14
Depression	Sertraline	40	Yes	1 2 3 4 5	25 17 7 3 48	2	15
Anxiety	Diazepam	52	Yes	1 2 3 4 5	23 11 6 6 54	2	16

time of the survey are listed in *Table 2*. *Table 2* shows a 60% agreement between respondents in regards to the number one medication used in each category, apart from anxiety, depression, dry mouth, and constipation.

The 20 most frequently nominated drugs and level of evidence are shown in *Table 3*.[1]

Discussion

The response rate of the survey was low, therefore we cannot be sure this represents Australian palliative care doctors. Nevertheless, a broad spectrum of palliative care doctors responded and our findings were similar to the international survey.[1] There were differences among the 20 essential drugs with only 10 common to both lists (the top eight, followed by diazepam and fentanyl). There are many possible explanations, including different availability and formulations, costs and different preferences (perhaps based on clinical experience rather than evidence). Laxatives such as lactulose are commonly prescribed worldwide, while in Australia, docusate and senna is most commonly prescribed. There is no evidence that adding docusate to senna provides benefit. Any difference between lactulose and senna appears to be minimal in the small amount of data available.[3]

There seems to be a relatively low level of evidence for some important medications in palliative care (eg. midazolam) although the majority of first ranked drugs have at least level 2 evidence. Apart from the most frequently used medications, there was a large discrepancy between the respondents' belief about the available evidence and what is actually available. For example paracetamol for pain, where level 1 evidence is available, but the majority of respondents rated evidence as levels 3–5, while more than one in 3 respondents thought morphine only had level 4 or 5 evidence for analgesia, whereas the evidence is level 2. About a third thought there was level 1–3 evidence for hyoscine hydrobromide (level 4) and midazolam (level 4).

We have used these lists to facilitate a process to increase their PBS listing with a group made up of the medical profession and the Rural Health and Palliative Care Branch of the Department of Health and Ageing in association with the Australian government. This has lead to a section in the PBS specifically for palliative care with an initial list of approved drugs.

For many widely used drugs the best level of evidence is not sufficient to justify further subsidy. Reasons may be that studies have not yet been undertaken – we should address this.

Implications for general practice

- Access to drugs for palliative care is harder in the community (through the PBS) than in hospital.
- A survey of palliative care doctors produced a list of drugs they thought essential.
- Their perception of the evidence for their use was variable.
- Collaborative work has led to the creation of the first ever section in the PBS for a specific patient population.
- There is a need for high quality studies to justify PBS listing of palliative care drugs.

Table 3. Ranking of 'essential' drug, compared with those of a previous world survey

Rank	Drug	Main palliative care indication	Rank number of a previous (world) survey[1]	Highest level of evidence	Current PBS listing (December 2005)
1	Morphine	Pain	1,* 5*	1 [17]	Yes
2	Haloperidol	Delirium	2	2 [14]	Yes
3	Dexamethasone	Anorexia/cachexia	4	2 [10]	Yes
4	Midazolam	Terminal restlessness	7	4 [9]	No
5	Metoclopramide	Nausea/vomiting	3	1 [18]	Yes
6	Clonazepam	Terminal restlessness	15	4E [12]	Yes
7	Paracetamol	Pain	9	1 [5]	Yes
8	Amitryptiline	Neuropathic pain	6	1 [19]	Yes
9	Pamidronate	Hypercalcaemia		2 [20]	Yes
10	Cyclizine	Nausea/vomiting		4E [12]	No
11	Hyoscine hydrobromide	Excess oropharyngeal secretions		3 [21]	No
12	Diazepam	Anxiety	17	2 [16]	Yes
13	Lorazepam	Anxiety		2 [22]	No
14	Omeprazole	Dyspepsia		1 [23]	Yes
15	Chlorpromazine	Delirium		2 [14]	Yes
16	Fentanyl[a]	Pain	12	1 [24]	Yes
17	Spironolactone	Ascites		4 [25]	Yes
18	Ranitidine	Dyspepsia		1 [26]	Yes
19	Promethazine	Nausea/itch		4E [12]	Yes
20	Frusemide	Ascites		4 [27]	Yes

a = injectable fentanyl not available on the PBS * = normal release + = sustained release

Conflict of interest: David Woods – speaker fees and travel assistance to attend meetings has been paid for by Mundipharma and Janssen-Cilag.

Acknowledgments

Thanks to the Australian and New Zealand Society of Palliative Medicine and Palliative Care Australia for funding, to Mary Brooksbank for research assistance, and the Department of Health and Ageing (National Cancer Strategies Group and A/Prof Rosemary Knight) for support.

References

1. Dickerson D. The 20 essential drugs in palliative care. European Journal of Palliative Care 1999;6:130–5.
2. National Health and Medical Research Council. Guide to the development implementation and evaluation of clinical practice guidelines. Available at www.health.gov.au/nhmrc/publications/pdf/cp30.pdf Accessed 13 January 2005.
3. Agra Y, Sacristan A, Gonzalez M, Ferrari M, Portugues A, Calvo MJ. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. J Pain Symptom Manage 1998;15:1–7.
4. Boureau F, Saudubray F, d'Arnoux C, et al. A comparative study of controlled release morphine (CRM) suspension and CRM tablets in chronic cancer pain. J Pain Symptom Manage 1992;7:393–9.
5. de Craen AJ, Di Giulio G, Lampe-Schoenmaeckers JE, Kessels AG, Kleijnen J. Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. BMJ 1996;313:321–5.
6. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ 1995;311:1047–52.
7. Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. Ann Intern Med 1993;119:906–7.
8. Bennett MI. Death rattle: an audit of hyoscine (scopolamine) use and review of management. J Pain Symptom Manage 1996;12:229–33.
9. Burke AL, Diamond PL, Hulbert J, Yeatman J, Farr EA. Terminal restlessness: its management and the role of midazolam. Med J Aust 1991;155:485–7.
10. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomised comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J Clin Oncol 1999;17:3299–306.
11. Bruera E, Seifert L, Watanabe S, et al. Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide based antiemetic regimen. J Pain Symptom Manage 1996;11:147–53.
12. Therapeutic Guidelines. Therapeutic guidelines: palliative care. Ver 1. North Melbourne: Therapeutic Guidelines, 2001.
13. Sweeney MP, Bagg J, Baxter WP, Aitchison TC. Clinical trial of a mucin containing oral spray for treatment of xerostomia in hospice patients. Palliat Med 1997;11:225–32.
14. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalised AIDS patients. Am J Psychiatry 1996;153:231–7.
15. Moller HJ, Gallinat J, Hegerl U, et al. Double blind, multicenter comparative study of sertraline and amitriptyline in hospitalised patients with major depression. Pharmacopsychiatry 1998;31:170–7.
16. Elie R, Lamontagne Y. Alprazolam and diazepam in the treatment of generalized anxiety. J Clin Psychopharmacol 1984;4:125–9.
17. Wiffen PJ, Edwards JE, Barden J, McQuay HJ. Oral morphine for cancer pain. Cochrane Database Syst Rev 2003;CD003868.
18. Glare P, Pereira G, Kristjanson LJ, Stockler M, Tattersall M. Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far advanced cancer. Support Care Cancer 2004;12:432–40.
19. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain 1996;68:217–27.
20. Purohit OP, Radstone CR, Anthony C, Kanis JA, Coleman RE. A randomised double blind comparison of intravenous pamidronate and clodronate in the hypercalcaemia of malignancy. Br J Cancer 1995;72:1289–93.
21. Back IN, Jenkins K, Blower A, Beckhelling J. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. Palliat Med 2001;15:329–36.
22. Laakmann G, Schule C, Lorkowski G, Baghai T, Kuhn K, Ehrentraut S. Buspirone and lorazepam in the treatment of generalized anxiety disorder in outpatients. Psychopharmacology (Berl) 1998;136:357–66.
23. Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. Cochrane Database Syst Rev 2003;CD001961.
24. Clark AJ, Ahmedzai SH, Allan LG, et al. Efficacy and safety of transdermal fentanyl and sustained release oral morphine in patients with cancer and chronic non-cancer pain. Curr Med Res Opin 2004;20:1419–28.
25. Greenway B, Johnson PJ, Williams R. Control of malignant ascites with spironolactone. Br J Surg 1982;69:441–2.
26. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev 2004;CD001960.
27. Pockros PJ, Esrason KT, Nguyen C, Duque J, Woods S. Mobilisation of malignant ascites with diuretics is dependent on ascitic fluid characteristics. Gastroenterology 1992;103:1302–6.

afp CORRESPONDENCE email: afp@racgp.org.au