PALLIATIVE MEDICINE: MY CONTRIBUTION TO THE
DEVELOPMENT OF AN EVIDENCE BASE

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Thesis presented for the degree of Doctor of Philosophy
University of Newcastle
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Declaration

I hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author; and endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

See Appendix 1

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Acknowledgements

This thesis has been an evolving (and at times arduous) journey. Like all journeys the final destination is not always where you think you will end up.

I would firstly like to acknowledge my supervisor - Professor Peter Ravenscroft. His gentle encouragement and feedback, has enabled me to reach this final destination. I would also like to acknowledge Professor Gerry Gleeson, who acted as a co-supervisor, until the journey changed direction a little, but in our talks I found a lot of help and inspiration.

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I am thankful that my parents valued giving their children a good education, and hope they learnt a bit along the way.

Finally I am grateful to all the patients I have cared for, who have taught me so much about life.
List of publications included as part of the thesis:


Medically Assisted Nutrition and Hydration


Clinical medications trials:


**Service Delivery**


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See Appendix 2

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Date ______________ 01/06/2012 ______________
List of additional publications


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Bibliography
Abbreviations:
ASCO - American Society of Clinical Oncology
DVT - deep vein thrombosis
ImPaCCT - Improving Palliative Care through Clinical Trials
MAH - medically assisted hydration
MAN - medically assisted nutrition
MANH - medically assisted nutrition and hydration
PACCSC - Palliative Care Clinical Studies Collaborative
PVC - Polyvinyl chloride
RCT(s) - randomised controlled trial(s)
Abstract:

Palliative Medicine is a challenging area of health care to work in and to perform quality research studies. The aim of Palliative Medicine is to apply the highest quality evidence to the problems encountered, taking into account the individual needs of the patient.

This thesis by publication consists of sixteen published, peer review articles, which have made an original and significant contribution to the knowledge base of Palliative Medicine. The first publication explored how much daily practice in Palliative Medicine was based on available evidence. It found that approximately half of interventions performed in an inpatient Palliative Care population were based on randomised controlled trials.

This led to research and publication in three different areas of Palliative Medicine.

The first was the difficult clinical and ethical dilemma of the use of medically assisted nutrition and hydration in Palliative Care. Two Cochrane systematic reviews were performed that found there were insufficient good quality studies to make any recommendations for practice with regard to the use of medically assisted hydration or medically assisted nutrition in Palliative Care patients. Three qualitative studies were undertaken, exploring the use of medically assisted nutrition and hydration at the end of life, in both the acute, and palliative care, setting. These found that Palliative Care doctors and nurses believed that medically assisted nutrition and hydration at the end stage of life rarely benefit patients and as long as adequate mouth care is given, patients do not suffer. However, family members do experience emotional distress in dealing with this situation. In the acute hospital setting the views of doctors in regards to medically assisted hydration represents a professional and personal struggle involved in attending to those who are dying and is accompanied by a discourse of uncertainty.
The second area of research was clinical medication trials, studying the use of a variety of medications in different clinical situations to examine their efficacy and safety. This was initially undertaken with prospective, observational studies. These found that a “burst” ketamine protocol was relatively safe and simple with a reasonable (50%) response rate. Further to this was the finding that a ‘burst’ triple agent approach was safe and effective during episodes of poorly controlled acute on chronic pain. The use of intranasal sufentanil was tested and found that it provided rapid onset, intense but relatively short lasting analgesia and it is an effective, practical, and safe option for breakthrough pain. Studies of medications used in syringe drivers were then performed using high performance liquid chromatography. The significant findings from the first study was dexamethasone and midazolam should not be combined in syringe driver solutions, as their combination leads to the significant loss of midazolam and perhaps more importantly this study also showed that cloudiness of a solution is not the only predictor of drug loss and that drug loss may occur even in solutions that remain clear at time of preparation. The second of these studies showed that there is significant loss of clonazepam when it is infused from syringe drivers through polyvinyl chloride tubing. The last of these studies related to medications found there was no association between the doses of opioids and sedatives on the last day of life and survival in an inpatient Palliative Care unit.

The final area was related to service delivery, and looking at how to improve quality of care. The first of these studies showed that the median length of survival (after enrolment on an Australian Palliative Care program) was 54 days. The final area of study was examining medication use in Palliative Medicine and produced a list of 20 essential medication as determined by Australian Palliative Medicine doctors, and the evidence in support of their use.
The implications of these findings as well as the future challenges of research are also explored in the concluding chapter. The underlying theme of this thesis is about contributing to the development of an evidence base in Palliative Medicine.
Chapter One

Overview
PREFACE

My initial training was in Internal Medicine. As a trainee it was imperative to know the latest studies and ‘evidence’ for a particular intervention – often around large cardiovascular trials. When I started Palliative Medicine training, on a consultant ward round we encountered a patient who had anorexia. The Consultant decided to start the patient on dexamethasone to stimulate appetite, and then said to me –“There is no evidence for that treatment, but we will see how we go”. I was a bit shocked and disappointed that I had started my specialist training in an area that was practicing medicine like this - supposedly prescribing medication, for which there was no evidence. Interestingly there was at least one randomised controlled trial published at the time that studied this question. That encounter was the starting point for this thesis – to investigate what evidence was available for the interventions we administered, as well as aiming to increase the evidence base in Palliative Medicine through performing studies with varying methodologies. There are two major challenges in decision making in Palliative care - one is finding the evidence for the best treatment, and the second is putting this ‘evidence’ within the context of the individual patient circumstances and their particular values. This can be even more challenging when there is little or no ‘evidence’ to guide clinical decision making.
1.1 Introduction:

This thesis by publications is a series of studies using different types of research methods – primary and secondary studies as well as quantitative and qualitative. (Figure 1)

It is arranged with an overview followed by fourteen chapters, each with a publication and finishing with a concluding chapter. The publications are presented in the format that they have been published in each journal. Each chapter/publication has its own literature review relevant to the article, as well as methodology and reference list.

Chapter two is a retrospective audit that examines the question:

“How much of a hospital-based Palliative Medicine practice was based on evidence from the literature?”

This publication was the basis for further research and publication under three main areas.

Medically assisted Nutrition and Hydration:

The first looks at both the difficult clinical and ethical dilemma of the use of medically assisted nutrition and hydration (MANH) in Palliative Care. There is probably no other area in Palliative Care where there have been such divisive views proposed on the best clinical approach, but regarding which there is very little high quality data. To address this question, two Cochrane systematic reviews were performed to try and analyse what was the highest quality evidence regarding MANH in Palliative Care – Chapters three and four. Chapter five uses qualitative methodology, to examine Palliative Care professionals’ experience of MANH, leading onto chapter six that examines the difficult clinical situations and chapter seven that documents the
experience of acute hospital doctors in the use of medically assisted hydration (MAH) at the end of life.

**Clinical medications trials:**

The second area is a series of clinical trials and experiments. Chapter eight is a study examining the use of ketamine in a Palliative Care setting. This was a prospective trial that built on a smaller previous study. Chapter nine is another prospective trial that examined the use of a novel approach - “triple agent therapy” - a combination of ketamine, opioid, and anti-inflammatory drug for difficult pain syndromes. Breakthrough pain remains one of the challenging areas to provide adequate analgesia. To try and improve the therapeutic options, chapter ten is a prospective, open label, observational study of intranasal sufentanil for cancer-associated breakthrough pain. Two further experiments are included in this area of research. The use of subcutaneous medications is very common in Palliative Care. The mixing of these medications has not been well studied, and most centres rely on visual incompatibility (cloudiness), or reporting of combinations to guide practice. To start to address these compatibility issues, both between medications and between medication and tubing two experiments were performed using high performance liquid chromatography. Chapter eleven examined the compatibility and stability of midazolam and dexamethasone in syringe drivers, whilst chapter twelve is a study of how different types of tubing effect the loss of clonazepam. Chapter thirteen is a study examining the association between the use of opioids and sedatives and the effect on survival (from hospice admission to death).

**Service Delivery**

The final area of research publications is in ‘service delivery”. The optimal timing of referrals to Palliative Care is still an area under study. Chapter fourteen explores how much time patients spend on a Palliative Care program in an Australian setting, as well
as comparing this to previously published studies from overseas. The final publication chapter is a study that used a survey to ask Palliative Medicine clinicians what medications they deemed essential in their practice.
Medically Assisted Nutrition and Hydration:
1. A discourse analysis of difficult clinical situations in relation to nutrition and hydration during end of life care.
2. Medical officers in acute care settings: their views on medically assisted nutrition and hydration at the end of life.
3. Medically assisted hydration for Palliative care patients.
4. Medically assisted nutrition for Palliative care in adult patients.
5. Palliative care professionals' perceptions of nutrition and hydration at the end of life.

Service Delivery:
1. Survival after enrollment in an Australian palliative care program
2. What are the essential medications in palliative care? A survey of Australian palliative care doctors

Clinical medications trials:
2. The compatibility and stability of midazolam and dexamethasone in infusion solutions.
5. Effects of opioids and sedatives on survival in an Australian inpatient Palliative care population
6. The effectiveness and adverse effects profile of "burst" ketamine in refractory cancer pain
1.2 Literature Review

1.2.1 Evidence-based medicine

“Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with best external clinical evidence from systematic research.” (1)

There has been much debate about what the benefits and pitfalls of trying to practice evidence based medicine. The issues start at the need to gather and assimilate the highest quality evidence, followed by working out how to apply that evidence to the individual patient. Evidence based medicine is based on finding the highest quality evidence and applying it to individual patients. There are many different ways to gather evidence in medicine.

1.2.2 Clinical Trial Methodology in Palliative Care

There are a variety of clinical trial methodologies. Each methodology has their advantages and disadvantages. Furthermore each have varying degrees of usefulness when trying to apply the findings to everyday practice (‘generalisability’).

1.2.2.1 Systematic Review

Systematic reviews of high quality RCTs are generally considered at the top of the hierarchy of evidence. (2) If these RCTs are homogenous in nature then a quantitative analysis of the results can be performed, leading to a meta-analysis. A meta-analysis aims to combine the data from individual studies, so as to increase the power of the analysis. It is reliant on having good quality RCTs (usually) from which to draw the data. The difficulty in the field of Palliative Medicine is that there are few (but an increasing
RCTs, that are able to be part of a systematic review. This limits the ability of systematic reviews to provide guidance for clinical practice.(3) However there are an increasing number of systematic reviews in the Pain, Palliative and Supportive Care section of the Cochrane database, but it is rare that any of these also have a meta-analysis included.(4)

1.2.2.2 Randomised Controlled Trials (RCTs)

RCTs are considered to be the gold standard approach to assessing intervention, because of their ability to minimise bias.(2) Through random allocation of participants to different intervention groups it is hoped that bias will be minimised and the study will produce an accurate, reliable and reproducible result. It is this ability to minimise bias, on which the quality of RCTs are judged.(5) Therefore it is important that randomisation is truly random (e.g. computer generated randomisation, hidden within sealed envelopes), so that an investigator recruiting patients will not be consciously or subconsciously influenced about whether to recruit or not. As well as this the intervention needs to be truly blinded to the participant and the investigator - i.e. neither knows which of the intervention arms the participant is in. This will minimise any bias in assessing effect or side effects of the intervention. As well, where possible all participants who are enrolled in the study are followed up, and reasons for dropout/withdrawal are stated – this is to minimise the bias, of having participants who have adverse effects withdrawing and data not being counted, or participants not thinking there is a benefit and withdrawing. Some of the weaknesses of RCTs are the fact that they aim to control the differences between the two groups so that any changes can be attributable only to the intervention. This can lead to very strict inclusion/exclusion criteria and make the generalisability of the results very limited. Given that the major reason for performing clinical trials is to improve health care of as many patients as possible, this is a major shortcoming of this trial design. It has been traditionally difficult to perform RCTs in Palliative Care patients, but recently there have been an increasing
number of successfully recruited trials.\textsuperscript{(6, 7)} If performed well, RCTs are a very powerful way of assessing the effectiveness of interventions.

A special form of RCTs are N of 1 trials. These are essentially randomised trials in individual patient, where the patient acts as their own control, and at the end of the study a result applicable to the individual is obtained. The intervention is given in pairs of treatment, in a randomised fashion (usually blinded), with the pattern repeated over several cycles. When this type of trial is performed in an individual patient, Guyatt et al. \textsuperscript{(8)}, argue that for that individual patient, this produces the highest level of evidence in a hierarchical model.

\textit{1.2.2.3 Observational Studies}

These approaches are based on clinical trials, yet there are other forms of research that can inform and improve practice. Examples of this include prospective observational studies, and non randomised interventional trials. One of the big weaknesses of these study designs are that they can be subject to considerable bias. The participant and investigator can both be aware of the intervention that is being received, and this can lead to a placebo effect (perceived benefit, that is not directly attributable to intervention). The placebo effect can be very high, especially in trials dealing with pain. \textsuperscript{(9)}

\textit{1.2.2.4 Qualitative Studies}

Qualitative research aims to develop an in depth understanding of the issues or experience in a clinical setting.\textsuperscript{(10)} It often tries to focus on “answering the questions of - ‘why?’ and ‘how?’”.\textsuperscript{(10)} As well it is more focussed on hypothesis generating rather than hypothesis testing. There have been attempts to try and incorporate this type of research into evidence-base gradings.\textsuperscript{(11, 12)}
Research methodology needs to be tailored and adapted to the problem and population studied. It is only through a spectrum of methodological approaches that evidence gathered is able to be applied to future individual patients.

1.2.3 Palliative Medicine – a special case?

“Palliative Medicine is the study and management of patients with active, progressive, far-advanced disease, for whom the prognosis is limited and the focus of care is the quality of life”. (13)

Palliative Medicine has been criticised for being slow in the development of evidence to guide its clinical practice. (14) Some of the early criticism of performing research on Palliative Care focussed around the “medicalisation” of dying. (15) With this was the idea that intervening and studying in a scientific way, would somehow cause a natural process to be medicalised. More recent commentary has centred around the ethics and morality of Palliative Care research. The initial reluctance to perform studies on terminally ill patients has shifted somewhat to talk about the “moral imperative” (16) to conduct studies so that we are no longer “experimenting” on Palliative Care patients. (17) This is based on the idea that generating higher quality evidence about interventions in Palliative Care will lead to an improvement in care of future patients.

There has been much written on the difficulties of doing research in the Palliative Care population. That includes the vulnerability of patients, as well as the fact they are often very sick, and there are concerns around the additional burdens of being involved in clinical trials. Sometimes patients in Palliative Care are seen as particularly ‘vulnerable’ by staff members and ethics committees. This has led to gatekeeping by staff, and slow processes to get trials through ethics committees. (18, 19) As well, death is often the natural outcome of a Palliative Care patients, whether on a trial or not, and this needs to be taken into account when looking at reporting of outcomes. (20)
Balanced against this is the fact that some surveys have found patients and carers are keen to be involved in trials, often with an altruistic aim to help others rather than themselves. (21) Recent approaches to clinical trials have aimed to overcome some of these challenges with multicentre enrolment, centralised web-based data recording, decreased recording burden, and innovative design. (22, 23) These include N of 1 studies that enable the patient to be both the control and participant, leading to lower numbers needed, as well as producing individual outcomes. However only a restricted number of medication interventions can use this method. (24) The medication that is being studied needs a short onset of action, as well as a short duration of action so that short cycle duration is possible. As well the condition being treated needs to be relatively stable, so that any changes across the various cycles can be attributed to the medication. An advantage of this methodology over RCTs is that the individual participant gets a result from participation in the trial, and is then able to either continue or stop the medication depending on the result.

This evidence based approach suits the style of clinical trials to find what is the best intervention, what are the side effects, or what is the most cost effective. However there are many areas of Palliative Medicine where it is not possible or desirable to conduct RCT. (25) Examples of this include learning about the patients experience or wishes, rather than studying interventions. These include learning about the experience of patients when being admitted into an inpatient Palliative Care unit, (26) preferences for treatment decisions (e.g., Deep Vein Thrombosis (DVT) prophylaxis (27, 28)), and the meaning of interventions. (29) Other areas where this has been particularly challenging have been in the use of medically assisted nutrition and hydration (MANH), sedation at the end of life, and interventional techniques.

The argument that Palliative Care patients do not or should not be included in research is no longer valid. Most studies have found that it is most patients’ wishes to be
included in studies if possible. The challenge is to do this in a sensitive and caring way.

1.2.4 Methodologies used in Palliative Medicine Research

Observational studies can be very useful to examine what is current practice, and look at benchmarking between services and Palliative Care units. It is through such observational studies that questions such as patterns of drug use as well as timing of referrals to Palliative Care have been studied. This helps clinicians examine their own practice and determine whether they are close to a benchmark, or far from it, leading to questions about how can practice be changed or improved. To answer some of these questions, there are several approaches, each yielding slightly different pieces of a jigsaw puzzle. For example to look at the issue of timing of referral to Palliative care. There is a presumption that patients are generally referred late in the course of their illness, and that earlier referral would be better. The first step is to look at the timing of referral and where it lies in the disease trajectory. Then test the hypothesis that earlier referral is better. Interestingly there has been very few studies looking at this, but one recent RCT did study this question in patients with metastatic non small cell lung cancer. There was a positive finding in this group of patients, but it will need to be replicated in a wider set of patients. Another approach may be to try and develop referral guidelines and criteria to encourage earlier referral from clinicians. A different approach is to use qualitative research to explore in depth what are the clinicians experiences and perceptions of referring to Palliative Care. Understanding what it is that initiates the clinician to refer may be the most important step to improving practice.

1.2.5 Publications in Palliative Medicine Research

There has been ever increasing number of citations in the Palliative Care literature. A recent study looked at the characteristics of this increase and found that there was both
an increase in the proportion of Palliative Care citations compared to the general medical literature, and an increase in the proportion of clinical trials within the Palliative Care literature. (32) Corresponding to this has been an increase in the number of systematic reviews produced in the Palliative and Supportive Care subsection of the Pain, Palliative and Supportive Care Group (n=82).(4)

This shows that more research is being performed in the area of Palliative Medicine. The challenge from this is to ensure that high quality studies are being performed and the research findings are being disseminated and adopted into practice and that this adoption leads to an improvement in the quality of care for patients and their carers.

Before clinicians look at implementing new practice, it is important to ensure their knowledge is up to date. With the rapid increase in trials and publications within Palliative Care it has become harder to be able to keep up with this ‘new knowledge’. (32) There are particular difficulties in the area of Palliative Care as there are large numbers of articles not stored on MEDLINE,(33) as well as a high proportion of information presented at conferences that does not make it into peer reviewed journals. (34) This could mean that there is a particular characteristic of this area of medicine that means the information is not published, or that the information presented is not of a sufficient standard to be published within a rigorous peer review process.

A different way of looking at translating research into practice is to examine or audit how much of an individual’s practice is based on evidence (the higher the quality the better). There have been few published studies in Palliative Medicine looking at how much of an individual’s practice is evidence based. One such trial was the starting point for this thesis.(35)
1.3 Aims of the thesis

The broad aim of this thesis was to contribute to improving the evidence base in Palliative Medicine through a series of studies, with varying methodologies.

The specific aims of the thesis were (with study methodology):

1. Assess how much of hospital based Palliative Care was evidence based (Chapter 2).
2. Perform a systematic review to summarise the current evidence for the use of MAH for Palliative Care patients (Chapter 3). Cochrane systematic review
3. Perform a systematic review to summarise the current evidence for the use of MAN for Palliative Care patients (Chapter 4). Cochrane systematic review
4. Document the experience of doctors and nurses working in Palliative Care, dealing with the provision and non-provision of MANH in terminally ill patients (Chapter 5). Qualitative methodology
5. Explore the challenges, nurses and doctors face when negotiating with families regarding nutrition and hydration at the end of life (Chapter 6). Qualitative methodology
6. Examine the perceptions of doctors in acute care settings regarding the use of MAH in end of life care (Chapter 7). Qualitative methodology
7. Assess the effectiveness and adverse effects of “Burst” Ketamine in refractory cancer pain (Chapter 8). Multi-centre, prospective open label study
8. Assess the efficacy and safety of a ‘multimodal’ approach for acute on chronic pain for Palliative Care inpatients (Chapter 9). Prospective audit
9. Demonstrate the efficacy, safety and patient acceptability of the use of intranasal sufentanil for cancer associated breakthrough pain (Chapter 10). Multi-centre, prospective, open-label, observational study.
10. Investigate the stability and compatibility of dexamethasone and midazolam combined in infusion solutions (Chapter 11). High performance liquid chromatography.

11. Investigate the effect of different tubing on loss of infused clonazepam using a syringe driver (Chapter 12). High performance liquid chromatography

12. Examine if there was any association between the use of opioids and sedatives and how long patients lived after admission to an inpatient Palliative Care unit (Chapter 13). Retrospective audit

13. Examine survival after enrolment in an integrated Palliative Care service and to determine what proportion of time, from diagnosis, is spent on a Palliative Care program (Chapter 14). Retrospective audit

14. Determine what Palliative Care doctors in Australia thought were essential medications in Palliative Care (Chapter 15). Questionnaire based in person and postal survey.
Chapter Two

Inpatient palliative medicine is evidence based

Chapter Two is published as:

**Introduction**

In 1995 a group of clinicians in Oxford studied how much of their inpatient general medicine practice was evidence based. (36) They found that 82% of their interventions were evidence based. This study used a similar methodology to examine how much an inpatient Palliative Medicine practice was evidence based. This paper was the first of its kind in the field of Palliative Medicine to explore the extent to which clinical practice was based on evidence. It showed that a lot of Palliative Medicine Practice was based on evidence, but as subsequent studies found, the quality of the trials was variable. (37)
Inpatient palliative medicine is evidence based

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Abstract: Specialist palliative care services have previously been studied to see whether their intervention is of benefit. However, there is a lack of data on whether interventions in individual palliative care units are evidence based. This study looked at 32 problems and 114 interventions over 1 month in January 2000 in an inpatient palliative care unit. These interventions were then researched to see if there had been trials showing their benefit. The results were then classified: 81% were evidence based (randomized controlled trials 48%, evidence from other trials 27%, convincing non-experimental evidence 6%). This compares favourably with studies performed in other areas of medicine.

Key words: palliative care; evidence-based medicine; randomized controlled trials; clinical trials; human; clinical medicine

Resumé: Savoir si l’intervention de services de soins palliatifs spécialisés est bénéfique, à déjà été étudié par le passé. Cependant, en ce qui concerne le fait de savoir si ces interventions basées sur des preuves, nous manquons de résultats. Cette étude s’intéressait à 32 problèmes et 114 interventions sur un mois en janvier 2000 dans une Unité de Soins Palliatifs. Nous avons ensuite cherché à savoir s’il y avait eu des essais cherchant à prouver les bénéfices de ces interventions. Nous avons ensuite classé les résultats de façon suivante: 81% étaient basé sur des preuves (essais randomisés contrôlés 48%, autres 27%, preuves convaincantes non expérimentales 6%). Ces résultats peuvent être comparés favorablement aux études réalisées dans d’autres secteurs de la médecine.

Mots-clés: soins palliatifs; médecine basée sur des preuves; essais contrôlés randomisés; essais cliniques; médecine clinique

Introduction

Evidence-based medical practice has been described as ‘integrating individual clinical expertise with the best available external clinical evidence from systematic research’.

Trials have been performed on whether care is improved with specialist palliative care units.

A previous study in general medicine found that 82% of their primary interventions were evidence based.

This study, using similar methodology, examined how much of a hospital-based palliative care practice was based on evidence from the literature.

Methods

The study was performed over a 4-week period from 10 January to 6 February 2000. All inpatients under one palliative care service and all subsequent admissions for the period of the study were included in the analysis. This was performed at...
the Mater Misericordiae Public Hospital in Brisbane, Australia. This is a university teaching hospital with a tertiary referral service for haematology and oncology. At that time, the palliative care service had inpatient beds in a haematology/oncology ward. At the end of the 4 weeks, for each patient, the main problems and subsequent interventions for those problems were agreed on by the consultant and registrar. Trials involving the interventions were then searched for on MEDLINE. The interventions were classified into

- I) intervention with evidence from randomized controlled trials;
- II) intervention with evidence from other trials;
- III) intervention with convincing non-experimental evidence;
- IV) intervention without substantial evidence.

## Results

During the 4-week period 23 inpatients were cared for in the palliative care service. There were 32 major problems and 114 different interventions (Table 1). The most common problem was hypercalcaemia and consequently the most common intervention was pamidronate with intravenous fluids. Fifty-five interventions (Table 2) had been shown in randomized controlled trials to be effective. This represents almost half of all interventions. Table 3 shows the results of interventions that had evidence from trials other than randomized controlled trials. These include comparative trials of small numbers that had individual crossovers, retrospective series, comparative studies, and uncontrolled or non-randomized studies. The most common problem in this group was subcutaneous morphine for pain.

Interventions that had convincing non-experimental evidence comprised 6% of the total (Table 4). These were interventions that were thought to be self-evident or ones in which randomized controlled trials would be difficult or unethical to perform. An example of this is the use of antibiotics to treat urinary tract infection or community acquired pneumonia.

There were 19% of interventions (Table 5) for which substantial evidence could not be found. The most common problem was constipation and the most common interventions were docusate for constipation and glycopyrrolate for control of oral secretions.

## Discussion

The majority of interventions (81%) were based on randomized controlled trials, other trials or convincing non-experimental evidence (Table 1). This includes 48% of interventions based on randomized controlled trials. This contrasts with the common misconception that a lot of palliative care is not based on any solid evidence. While 19% of interventions were found not to be based on substantial evidence, we realize the difficulty in retrieving all relevant trials. Consequently, we would be most pleased to be corrected if people know of trials showing that these interventions are effective. This compares favourably with a study performed in inpatient general medicine.

There are many people asking for more research into the area of palliative care. This study looked at the evidence for routine practice within a palliative care service and found that there have been randomized controlled trials in many areas of palliative care, but that substantial areas are still deficient. An example of one such area is constipation. It is one of the most common symptoms in people with advanced cancer, with an incidence of up to 71%, yet there are very few randomized controlled trials in this area.

Another area of difficulty in this field is that many people with cancer are excluded from clinical trials. One example can be seen in people with brain tumours who have had seizures. While a trial has been done to show prophylactic anticonvulsants are not of benefit, little prospective research has been done to look at what is the best treatment for patients who have had a seizure who also have an incurable brain tumour.

### Table 1 Summary of results

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>I) Intervention with evidence from randomized controlled trials</td>
<td>55 (48%)</td>
</tr>
<tr>
<td>II) Intervention with evidence from other trials</td>
<td>31 (27%)</td>
</tr>
<tr>
<td>III) Intervention with convincing non-experimental evidence</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>IV) Intervention without substantial evidence</td>
<td>21 (19%)</td>
</tr>
</tbody>
</table>
While many trials in the area of pain have been done, there is still a lack of compelling evidence for the use of dexamethasone and subcutaneous ketamine. This seems particularly important as ketamine is often used in neuropathic pain that is otherwise difficult to control. This is not to say they are both ineffective – we have found them very useful in individual patients. Rather what is lacking

### Table 2 Intervention with evidence from randomized controlled trials (n = 55)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Intervention</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcaemia</td>
<td>Pamidronate and intravenous fluids</td>
<td>8</td>
<td>21,22</td>
</tr>
<tr>
<td>Pain</td>
<td>Clodronate</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Pain</td>
<td>Morphine slow-release oral</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Pain</td>
<td>Morphine spinal</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Pain</td>
<td>Fentanyl subcutaneous</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>Pain</td>
<td>Bupivacaine intrathecal</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Dexamethasone</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Constipation</td>
<td>Lactulose</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>Constipation</td>
<td>Senna</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Constipation</td>
<td>Polyethylene glycol</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>Cerebral tumour, symptomatic</td>
<td>Dexamethasone</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>Bone metastasis, pain</td>
<td>Radiotherapy</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Bone metastasis, pain</td>
<td>Samarium</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Oropharyngeal candidosis</td>
<td>Nystatin</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>Oropharyngeal candidosis</td>
<td>Ketoconazole</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Amitriptyline</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Sodium bicarbonate</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Insulin/dextrose</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Atrial fibrillation with rapid</td>
<td>Digoxin</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>ventricular response</td>
<td>Amiodarone</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Nausea due to radiotherapy</td>
<td>Ondansetron</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Dexamethasone</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Metoclopramide</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Ondansetron</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Valaciclovir</td>
<td>1</td>
<td>43</td>
</tr>
<tr>
<td>Depression</td>
<td>Paroxetine</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>Haematemesis</td>
<td>Omeprazole</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>Dexamethasone</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>Radiotherapy</td>
<td>1</td>
<td>47</td>
</tr>
</tbody>
</table>

### Table 3 Intervention with evidence from other trials (n = 31)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Intervention</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Morphine subcutaneous infusion</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Pain</td>
<td>Fentanyl transdermal</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Pain</td>
<td>Ketamine intrathecal</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Delirium</td>
<td>Midazolam</td>
<td>5</td>
<td>7,8</td>
</tr>
<tr>
<td>Delirium</td>
<td>Haloperidol</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Haloperidol</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Blood transfusion</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Morphine subcutaneous</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Morphine nebulized</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>Calcitonin</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Fractured long bone</td>
<td>Intramedullary nail</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Fractured long bone</td>
<td>Radiotherapy</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>
both cases is prospective, randomized (or crossover) trials to conclusively show their effectiveness.

Palliative medicine is considered both an art and a science. Arguably, treatment is tailored to the individual patient and their support group more than in any other area of medicine. This can sometimes mean treatment does not conform to guidelines used in other areas of internal medicine. While it is hard to know if our experience of this month is applicable to other palliative care inpatient units, it does show that, in this inpatient setting, palliative medicine practice is evidence based.

**Conflicts of interest**

This study was not funded and there was no conflict of interest.

**References**

Inpatient palliative medicine is evidence based


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Medically assisted hydration for adult palliative care patients

Chapter Three is published as:
Introduction

The next two chapters are trying to determine the best evidence for the use of medically assisted nutrition and hydration at the end of life. It is an area of medicine that has often drawn strong diametrically opposed views, for which there seems few high quality studies. To determine what high quality studies were available to base ethical arguments on, two Cochrane reviews were undertaken, with one being recently updated. The Cochrane process involves developing a protocol that is peer reviewed, and then following that protocol to a full review (again peer reviewed). These reviews are then continuously updated. This has led to the publication of two protocols followed by the full reviews and one update (hydration).

The paper in this chapter is the first systematic review of available high quality studies to guide the controversial practice of medically assisted hydration at the end of life. It identified five relevant studies, but a meta analysis was not possible due to small number of studies and heterogeneity of data. It showed that there was a lack of high quality studies available to guide practice and that further research was needed.
Medically assisted hydration for adult palliative care patients
(Review)

Good P, Cavenagh J, Mather M, Ravenscroft P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library
2011, Issue 3

http://www.thecochranelibrary.com
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**ABSTRACT**

**Background**

Many palliative care patients have reduced oral intake during their illness. The management of this can include the provision of medically assisted hydration with the aim of prolonging the length of life of a patient, improving their quality of life, or both. This is an updated version of the original Cochrane review published in Issue 2, 2008.

**Objectives**

To determine the effect of medically assisted hydration in palliative care patients on their quality and length of life.

**Search strategy**

Studies were identified from searching CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT, Caresearch, Dissertation Abstracts, SCIENCE CITATION INDEX and the reference lists of all eligible studies, key textbooks, and previous systematic reviews. The date of the latest search conducted on EMBASE, CENTRAL and MEDLINE was November 2010.

**Selection criteria**

All relevant randomised controlled trials (RCTs) or prospective controlled studies of medically assisted hydration in palliative care patients.

**Data collection and analysis**

Five relevant studies were identified. These included two RCTs (93 participants), and three prospective controlled trials (360 participants). These were assessed independently by two review authors for quality and validity. The small number of studies and the heterogeneity of the data meant that a quantitative analysis was not possible, so a description of the main findings was included only.

**Main results**

One study found that sedation and myoclonus (involuntary contractions of muscles) were improved more in the intervention group (28 - hydration, 23 - placebo). Another study found that dehydration was significantly higher in the non-hydration group, but that some fluid retention symptoms (pleural effusion, peripheral oedema and ascites) were significantly higher in the hydration group (59 - hydration group, 167 - non-hydration group). The other three studies did not show significant differences in outcomes between the two groups.
Authors’ conclusions
Since the last version of this review no new studies were found. However there is one ongoing, high quality study that has not reached full recruitment. There are insufficient good quality studies to make any recommendations for practice with regard to the use of medically assisted hydration in palliative care patients.

**PLAIN LANGUAGE SUMMARY**

Medically assisted hydration to assist palliative care patients

This review is an updated version of the original Cochrane review published in Issue 2, 2008, there has been no change to the conclusions since the first version was published. It is common for palliative care patients to have reduced fluid intake during their illness. Management of this condition includes discussion with the patient, family and staff involved and may include the provision of fluids with medical assistance. This can be performed using a small plastic tube inserted into a vein or subcutaneous tissue, or via a tube inserted into the stomach. It is unknown whether this treatment helps people to feel better or live longer. A search of the international literature was only able to find a small number of studies looking at this issue. As a result, it is not possible to clearly define the benefits and harms of this treatment.

**BACKGROUND**

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 2, 2008) on “Medically assisted hydration for adult palliative care patients” (Good 2008b). Many palliative care patients have a reduced oral intake during their illness. The cause of this varies, but may be partly due to a physical obstruction, anorexia/cachexia syndrome, generalised weakness, bowel obstruction, nausea, decreased level of consciousness, loss of desire to drink or no specific cause may be identified. The most common time for this decreased oral intake is during the terminal phase, when the patient becomes less conscious and therefore less able to receive fluids orally (Morita 1998).

Management of this condition includes discussion with the patient, family and staff involved and either no medical intervention (but continued attention to treating any symptomatic problems, including good mouth care) or the provision of hydration with medical assistance. The aim of medically assisted hydration can be to prolong the length of life of a patient, improve their quality of life, or both. These benefits may come via the reversal of the physiological factors associated with the patient’s decline. Balanced against these potential benefits are adverse events that can be associated with any intervention (infection, bleeding, pain, etc) (Bozzetti 1996).

Medically assisted hydration is usually performed via the intravenous or subcutaneous routes (parenteral), but can also use enteral routes. There is great variation in practice with regards to hydration, a Canadian study by Lanuke 2003 found that the rate of provision of medically assisted hydration differed greatly across the country (range 0 to 100%). There is controversy about the ethical aspects of medically assisted hydration (Casarett 2005). The first ethical controversy centres around whether medically assisted hydration is a medical intervention or a basic provision of comfort. Secondly there is controversy as to how and by whom should decisions be made with regards to medically assisted hydration in patients who no longer have the capacity to make decisions for themselves. This review will concentrate on assessing the benefit of provision of hydration with medical assistance versus the harm caused by such intervention in palliative care patients. It is only with this information that clinicians and patients can make informed decisions about whether this type of intervention is beneficial or harmful to an individual patient.

There has been a separate review looking at medically assisted nutrition for palliative care patients (Good 2008a).

**OBJECTIVES**

The objectives of this review are to determine the effect of medically assisted hydration in palliative care patients on their quality and length of life.
METHODS

Criteria for considering studies for this review

Types of studies
All relevant randomised controlled studies (RCTs) or prospective controlled studies that fulfilled the following criteria.

Types of participants
Participants included:
• palliative care participants who received medically assisted hydration;
• those that were receiving palliative care (WHO 2005);
• (but were not limited to) incurable cancer, dementia, neurodegenerative diseases (e.g. Motor Neuron Disease), Human Immunodeficiency Virus, Chronic Airways Limitation and Chronic Heart Failure;
• whose prognosis was limited and the focus of care was quality of life (Doyle 2004); and
• adult participants aged 18 years and above were included, both male and female and in any setting such as home, hospice or hospital.

Included participants were not limited to those in the terminal phase of their illness. Participants who were having medically assisted hydration as part of a perioperative, chemotherapy or radiotherapy regime, or because of chemotherapy or radiotherapy adverse effects were excluded.

Types of interventions

Medically assisted administration of fluids:
• medically assisted hydration - administration of non nutritional fluids, administered via the subcutaneous tissue, venous system or enterally (nasogastric tube, jejunostomy, gastrostomy).

Comparisons:
• placebo,
• no intervention,
• usual treatment or supportive care.

Types of outcome measures

Primary outcomes
1. Quality of life on any measure (including symptom assessment scales).

Secondary outcomes
1. Survival.
2. Adverse Events.

Search methods for identification of studies

Electronic searches
The following electronic databases were searched using a search strategy developed for MEDLINE via OVID, but were modified appropriately for each database. Please see Appendix 1 for the MEDLINE search strategy.
• The Cochrane Library: Cochrane Pain, Palliative & Supportive Care Register, the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Cochrane Database of Reviews of Effectiveness (searched up to Issue 11, 2010).
• MEDLINE (1966 to February 2010).
• EMBASE (1980 to February 2010).
• CINAHL (up to February 2008).
• CANCERLIT (up to February 2008).
• Caresearch - database listing conference proceedings and grey literature (up to February 2008).
• Dissertation abstracts (up to February 2008).
• SCIENCE CITATION INDEX (up to February 2008).

Searching other resources

Reference lists
The reference lists of all eligible studies, key textbooks, and previous systematic reviews were searched for additional studies.

Language
The search attempted to identify all relevant studies irrespective of language. There were no non-English papers identified.
Data collection and analysis

Selection of studies
Studies identified by the search strategy had the title and abstract (where possible) assessed by the lead review author (PG) to identify potentially relevant studies. The full text of potentially relevant studies, were retrieved and assessed independently by two review authors (PG and MM) with regards to inclusion criteria and quality. 

The results of studies identified from the different databases were as follows:

- The Cochrane Library - 167 (60 from clinical trials)
- MEDLINE - 1230
- EMBASE - 421
- CINAHL - 3
- CANCERLIT - 46
- Caresearch - 40
- Dissertation abstracts - 36
- SCIENCE CITATION INDEX - 797

After reviewing the titles and abstracts, 40 studies were retrieved in full, with a further review of the full text leading to seven being assessed by two review authors. After review of these articles, two were excluded, leaving five studies for inclusion.

The original search was performed in October 2006, and repeated in February 2008 prior to publication of the full review. Subsequent searches were run on November 2010 for the update of this review with the following results:

- MEDLINE 2008 to November week 1, 2010 - 158
- EMBASE 2008 to 2010 week 45 - 663
- CENTRAL Issue 4, 2010 - 205

There were no new completed studies identified from the most recent searches.

Data extraction and management

Data extraction
The following information was obtained for each study:

1. study methods (study design, allocation, blinding, setting, inclusion criteria);
2. participants (sample size, exclusions/inclusions, number, disease, duration of study, withdrawals and dropouts, site - e.g. hospital, hospice, home);
3. intervention (type, route of delivery, control used);
4. outcome (quality of life, symptom measures, survival, time from death intervention was initiated); and
5. adverse effects.

This extraction occurred independently by two review authors (PG and MM).

Quality
The five studies retrieved had their methodological quality assessed. Two were RCTs, and their quality was assessed via the Oxford Quality Scale (Jadad 1996). This scale uses the following questions to rate the likelihood of bias (the higher the score the less likelihood of bias, scale of zero to five).

- a. Was the study described as randomised (one = yes; zero = no)?
- b. Was the study described as double-blind (one = yes; zero = no)?
- c. Was there a description of withdrawals and dropouts (one = yes; zero = no)?
- d. Was the method of randomisation well described and appropriate (one = yes; zero = no)?
- e. Was the method of double-blinding well described and appropriate (one = yes; zero = no)?
- f. Deduct one point each if methods for randomisation and blinding were inappropriate.

Scoring system: maximum score = five; minimum score = zero.

Two studies were prospective controlled trials and their methodology was assessed using a scale devised by Rinck et al (Rinck 1997).

a. Quality criteria - accrual of the study population.
b. Homogeneity and participant characteristics.
c. Randomisation.
d. Attrition and sample size.
e. Interventions.
f. Outcome measurement.
g. Presentation of results.

Score one point if criteria fully applied
Score 0.5 point if criteria was not fully applied
Score 0 if criteria (mostly) not applied

Scoring system: maximum score = 7, minimum score = 0.

The results for each included study is reported in the 'Characteristics of included studies' table.

Data analysis
It was hoped there would be sufficient data and homogeneity between studies to allow pooling of results. However, there were only two RCTs identified, and only a small number of participants recruited to these studies. The heterogeneity of the data meant that a quantitative analysis was not possible. A description of the main findings from the studies is presented in the 'Results' section.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
The search for this update was run in November 2010, there were no new studies identified, however, there was one relevant ongoing study identified, that had been presented at a conference (Bruera 2010). For the original search seven studies appeared to meet the inclusion criteria (Bruera 2005; Cerchietti 2000; Morita 2002; Morita 2006; Morita 2005; Waller 1994; Viola 1997). On further review two studies were excluded (Morita 2002; Morita 2006). One study (Morita 2002) was excluded because there was no comparison between the groups with regards to hydration. Another study (Morita 2006) was excluded because there was no comparison between the symptoms of the hydrated and non-hydrated groups. Out of the remaining five studies, two were RCTs (Bruera 2005 (51 participants); Cerchietti 2000 (42 participants)), and three were prospective controlled trials (Morita 2005 (226 participants); Waller 1994 (68 participants); Viola 1997 (66 participants)).

Study design
Two studies (Bruera 2005; Cerchietti 2000) had a RCT design. The study duration of these was two days. The other three studies (Morita 2005; Waller 1994; Viola 1997) had a prospective controlled trial design. The study conducted in Japan by Morita 2005 had a study duration of three weeks, whilst the study by Waller 1994 was from admission to a hospice until death and Viola 1997 was from enrolment in the study until death, discharge or no longer having a fluid deficit.

Study population
All of the studies included only participants with advanced cancer. Three studies (Bruera 2005; Cerchietti 2000; Viola 1997) only included participants in whom it was thought the participants were dehydrated.

Intervention
In all of the studies the intervention group was aimed at having at least 1000 ml of fluid per day. The route of this varied between intravenous and subcutaneous.

Outcomes
The outcomes measured in all the studies was very different:
- Waller 1994 looked only at the state of consciousness.
- Bruera 2005 had a main outcome measure as the global assessment of the overall benefit of hydration to the participant, as determined by the physician and participant on day two. This was supplemented by a number of secondary outcome measures. These included symptom assessment scales used for sedation, fatigue, hallucinations, myoclonus, symptoms totaled together and the mini mental status examination (MMSE). These symptoms were scored on a numerical rating zero to ten scale, with a decrease of one point seen as an improvement (this was defined by the authors and it is unclear whether this is a statistical or clinical improvement).
- Cerchietti 2000 primarily looked at the symptoms of thirst, chronic nausea, delirium and changes in MMSE. Included in this study were the secondary outcome measures of anguish and mood.
- The observational study of Morita 2005 examined dehydration, fluid retention (ascites, bronchial secretions, peripheral oedema), hyperactive delirium, myoclonus, bedsores, agitation and communication capacity.
- The study by Viola 1997 looked at the prevalence of multiple physical symptoms and cognition.
- The two RCTS (Bruera 2005; Cerchietti 2000) looked at adverse effects of medically assisted hydration including local adverse effects (discomfort, pain, infection, oedema, erythema, bleeding at the puncture site) and interruption of hydration due to adverse effects (oedema, increase in respiratory secretions, congestive heart failure).

None of the studies looked at survival as an outcome measure, although the Canadian study (Viola 1997) reported length of survival after enrolment. There was no statistical analysis performed to see if there was any significant difference between the two groups in this study.

Risk of bias in included studies
The included studies were assessed by two independent review authors using two different quality scales. There were two RCTs and they were assessed using the Oxford Quality Scale (Jadad 1996). One of the RCTs (Bruera 2005) scored five out of five on this scale as it was a well designed and performed study. In particular the methods of randomisation and blinding were well described and appropriate. However, the other RCT (Cerchietti 2000) scored only two out of five, as the method of randomisation was not described, neither was whether any blinding was performed. The other three studies were prospective controlled trials and their quality was assessed using the Rinck scale (Rinck 1997). One of these, Morita 2005 scored 4.5 out of a maximum of seven on this scale. Its strengths were that consecutive participants were asked to be enrolled and a good description of baseline characteristics and follow-up was given. However, allocation was via physician preference thus introducing an element of bias, and also there was no planning of allocation to scoring of outcomes. The aim of the allocation according to physician preference was to try and mimic real world decision making. The study by Waller 1994 was subject to many methodological problems. There was inadequate inclusion and recruitment strategy, a poorly defined control group, no baseline data presented for groups, the length of time and composition of intravenous fluids was not included. This paper scored 1.5 out of seven on the Rinck scale. The third prospective study (Viola...
Medically assisted hydration for adult palliative care patients (Review)

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1997) scored four out of seven on the Rinck scale. This study was well designed, but the major shortcoming was in recruitment and performance of the study. Recruitment was performed at two different centres, and the two groups at baseline had many differences including type of cancers and symptom assessment scores. This meant that we were not able to make a true comparison between the group receiving medically assisted hydration and the control group receiving no medically assisted hydration in any of the outcome measures.

Effects of interventions

Effectiveness

One study (Bruera 2005) found that sedation and myoclonus were more greatly improved in the intervention group. In addition, if the total scores for the four target symptoms (sedation, fatigue, hallucinations, myoclonus) were taken as a whole, there was more improvement in the intervention group. The secondary outcome measure used in the Bruera 2005 study (proportion of participants perceived to have some benefit was equal to or greater than 50%) was significant in the hydration group in the view of the physicians but not the participants viewpoint. In another study (Cerchietti 2000), it was stated that “control of chronic nausea after 24 hours was significantly better in the group receiving hydration”. However, the results were never tabulated, but rather presented in a graphical form, and this actually showed the two groups almost equal after 24 hours, and the non-hydration group improving more than the hydration group in terms of lowering the VAS for chronic nausea. There were no significant differences found in all the other outcomes looked at in four other studies (Bruera 2005; Cerchietti 2000; Morita 2005; Waller 1994) in terms of effectiveness of medically assisted hydration. The fifth study (Viola 1997) only provided descriptive statistics, and so a comparison between the groups was not possible.

Adverse events

In terms of local adverse reactions Bruera 2005 reported no differences between the groups, but Cerchietti 2000 found there was one participant with erythema and pain at puncture site in the intervention group. Morita 2005 found that dehydration was significantly higher in the non-hydration group, and that some fluid retention symptoms (pleural effusion, peripheral oedema and ascites) were significantly higher in the hydration group.

Discussion

The objective of this systematic review was to determine the effect of medically assisted hydration in palliative care patients on their quality and length of life. Extensive searching of the literature produced only five studies suitable for inclusion. This included two RCTs. One of these (Bruera 2005) was of high methodological quality, but was not able to recruit sufficient participants to adequately power the study, whilst the other (Cerchietti 2000) had methodological flaws in design and reporting of results. Both these studies were of short duration of hydration (two days), and did not look at the effect on survival. Of the three prospective controlled studies, one was of reasonable quality (Morita 2005), whilst another (Waller 1994) had methodological shortcomings in design and reporting. The third prospectively controlled trial (Viola 1997) had a good methodological basis, but unfortunately the two groups recruited had many differences at baseline. There was also no statistical analysis of the results to determine if any differences were significant. The participants included in these studies represent a “narrow” palliative care population in that they all have cancer that is defined as ‘advanced’ or ‘terminal’. It is questionable whether the results of these studies would be generalisable to a wider palliative care population, especially those who do not have cancer.

For this update, in 2011, no new completed studies were identified. There was one relevant ongoing study identified, that had been presented at a conference (Bruera 2010) and it is hoped this will provide more evidence for a future update of this review.

So far the results of the studies included suggest that medically assisted hydration in palliative care patients may have some benefits in terms of improving sedation and myoclonus, and a perception of overall benefit. Hydration may also cause some adverse effects in terms of fluid retention (in particular pleural effusion, peripheral oedema and ascites). However, these results must be taken within the context of low participant numbers and methodological difficulties in the studies.

There has been much debate and varying views about the provision of medically assisted hydration to palliative care patients (Ashby 1995; Craig 1994). This review shows that there have been very few studies looking at the symptom benefits, and adverse effects of such an intervention.

Authors’ conclusions

Implications for practice

Since the last version of this review no new studies were found. However there is one ongoing, high quality study that has not reached full recruitment (Bruera 2010).

Currently there are insufficient good quality studies to make any recommendations for practice with regards to the use of medically assisted hydration in palliative care patients.

There are a few good quality studies that look at the benefits and harms of the use of medically assisted hydration in this popula-
Medically assisted hydration for adult palliative care patients (Review)

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Implications for research

Study design

High quality studies in the palliative care population have proven very difficult to perform successfully. The difficulty of research in a vulnerable population such as palliative care patients has been discussed in the literature. These difficulties start with consent, are followed by recruitment, elimination of confounders and end with retention of participants throughout a study period (Rinck 1997). There have been some innovative suggestions about how to overcome the issue of consent (Rees 2003) and some studies have used this methodology with success (Breitbart 2002). Others have shown that large numbers are not always needed to show a benefit (Abernethy 2003), but the question of safety is difficult to answer due to small numbers commonly being found in palliative care studies. This has been illustrated by the fact that there was only one RCT of a high quality in this review. Despite being methodologically sound the results were limited by lack of recruitment. Perhaps of more interest was the fact that the issue of medically assisted hydration in palliative care patients causes such divergent views, yet there are so few studies to guide clinical practice properly. As well as looking at further RCTs in this area, the evidence base will be improved with at least more prospective controlled trials.

Participant groups

The studies in this review had narrowly defined patient populations. Palliative care is performed in hospitals, inpatient palliative care units and in the community. Studies need to be performed in all these areas to allow external validity to different palliative care populations. It would also be helpful to define at what stage of their illness participants are being given medically assisted hydration. The reasons and aims of hydration in the last few days/weeks of life may be very different to those participants with a longer prognosis. Also all the participants in the included studies had advanced cancer, and it is important to look at medically assisted hydration in non-cancer populations. The prospective prediction of prognosis is difficult, and it may be better to stratify participants according to their performance status.

Interventions

Medically assisted hydration can be given by many different routes. The studies included in this review used either the subcutaneous or intravenous route. No studies were found that used the enteral route for hydration. Further studies are needed to determine the optimum route and dose.

Outcomes

It is important that clinically relevant outcomes are clearly defined and are the most clinically useful. In this patient population, this should include symptoms (such as sedation, fatigue, hallucinations and myoclonus) as well as diagnoses such as delirium. Despite much controversy about the effect medically assisted hydration may have on length of life, it was not an outcome looked at in any of the studies in this review. Future studies could include the survival of participants as an outcome. It is equally important that adverse events are well defined so that the risk of treatment can be balanced against any benefits.

Acknowledgements

Thank you to the peer referees for their helpful comments and to Sylvia Bickley, Trials Search Co-ordinator of the Cochrane Pain, Palliative and Supportive Care Review Group, for her help with the original search strategy, as well as Jane Hayes, Trials Search Co-ordinator of the Cochrane Pain, Palliative and Supportive Care Review Group for performing the most recent search in November 2010.
References to studies included in this review

**Bruea 2005** [published data only]

**Cerchietti 2000** [published data only]

**Morita 2005** [published data only]

**Viola 1997** [published data only]

**Waller 1994** [published data only]

References to studies excluded from this review

**Morita 2002** [published data only]

**Morita 2006** [published data only]

References to ongoing studies

**Bruea 2010** [published data only]

Additional references

**Abemethy 2003**

**Ashby 1995**

**Bozzetti 1996**

**Breitbart 2002**

**Casaret 2005**

**Craig 1994**
Craig GM. On withholding nutrition and hydration in the terminally ill: has palliative medicine gone too far?. *Journal of Medical Ethics* 1994;20(3):139-43; discussion 144-5. [DOI: 0306–6800 (Print)]

**Doyle 2004**

**Good 2008a**

**Jadad 1996**

**Lanuke 2003**

**Morita 1998**
Rees 2003

Rinck 1997

WHO 2005

References to other published versions of this review

Good 2008b

* Indicates the major publication for the study
**CHARACTERISTICS OF STUDIES**

**Characteristics of included studies** [ordered by study ID]

**Bruera 2005**

| Methods | Randomised, controlled, and double blind trial.  
|         | Method of randomisation is truly random.  
|         | Study duration - two days  
|         | Multicentre study |

| Participants | Participants with a diagnosis of advanced cancer, defined as locally recurrent or metastic, with no further treatment planned.  
|              | An oral intake of less than 1000 mL/d, as determined by clinical assessment; and evidence of mild to moderate dehydration, exhibited by decreased turgor in the subclavicular region lasting more than two seconds.  
|              | In addition, participants had to have one or more of the following findings: dry mouth; thirst; decreased volume of urine output, as reported by the patient; a darker colour of urine than usual, in the absence of reasons for jaundice or hematuria; and laboratory values consistent with dehydration, such as an elevated blood urea nitrogen to creatinine ratio of more than 20:1, when this value was obtained within 24 hours of admission to the study.  
|              | Finally, participants had to be older than 16 years, able to understand and give consent for participation in the study, and able to tolerate parenteral treatment and the application of a subcutaneous or intravenous cannula.  
|              | Sample size - 74 (13 - not eligible, 10 - refused)  
|              | 51 recruited |

| Interventions | 28 - Treatment - (1 withdrawal) - 1000 mls normal saline as an infusion over four hours for two days  
|               | 23 - placebo - (one withdrawal) - 100 mls normal saline as an infusion over four hours for two days  
|               | IV if IV in (12) - subcutaneous if no IV access (37) |

| Outcomes | The main outcome was the global assessment of the overall benefit of hydration to the participant, as determined by the physician and patient on day two - no statistically significant difference between groups.  
|          | Secondary method of analysis was to test the two groups separately to determine whether the proportion of patients perceived to have some benefit was equal to 50% or greater than 50% - Intervention group - P = 0.0035, Placebo group - P = 0.20  
|          | Target symptoms - numerical rating scale 0-10, with a decrease of one point seen as an improvement.  
|          | Sedation - more improvement in intervention group (P = 0.005)  
|          | Fatigue - no differences  
|          | Hallucinations - no differences  
|          | Myoclonus - more improvement in intervention group (P = 0.035)  
|          | Symptoms totaled together - more improvement in intervention group (P = 0.06)  
|          | MMSE - no differences in groups  
|          | Adverse effects - Pain at injection site, injection site swelling - no differences between groups |

| Notes | Oxford score - five  
|       | Some differences in performance status at randomisation, with intervention group have more participants in performance status 0, I, II  
|       | Study was underpowered, as recruitment was less than expected |
### Risk of bias

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### Cerchietti 2000

**Methods**
- Randomised, comparative and prospective.
- Method of randomisation not clear.
- Blinding status unclear
- Study duration - 48 hours
- Single centre

**Participants**
- Terminal stage advanced cancer patients, one or more of the following symptoms: thirst; chronic nausea or delirium; dehydration diagnosed on physical examination, with or without renal failure; and inability to maintain an adequate water intake (less than 50 ml/day fluid).
- Sample size - 50
- Non participation:
  - four - uncontrolled symptoms (pain in two of the participants, severe dyspnoea in another two),
  - One - bowel obstruction syndrome requiring surgery three - severe constipation (three participants)

**Interventions**
- 42 patients
  - 20 - treatment - 1000 ml 5% dextrose in water infusion with the addition of 140 mEq/l sodium chloride per day, at an infusion rate of 42 ml/h via the subcutaneous route.
  - 22 - usual treatment, with no subcutaneous fluids given

**Outcomes**
- Primary Outcome measures (VAS)
  1. Thirst
  2. Chronic nausea
  3. Delirium
  4. MMSE
- The results were not tabulated, and some graphs were given. The authors stated “that 1000 ml/day subcutaneous hydration does not improve control of the assessed symptoms when added to the general and pharmacological treatment in patients with end-stage cancer. However, control of chronic nausea after 24 hours was significantly better in the group receiving hydration.”
- However, the graph of this actually shows the two groups both improving and the non hydration group improving more in terms of the VAS
- Secondary outcome measures
  1. Anguish (measurement not defined) - no differences in groups
  2. Mood (measurement not defined) - no differences in groups
  3. Interruption of hydrations (oedema, increase in respiratory secretions, congestive heart failure)
  4. Local adverse reactions - n = 1, erythema and pain at puncture site, 36 hours after start of treatment

**Notes**
- Oxford score - two
- Median survival close to four days in both groups
### Morita 2005

**Methods**
- Prospective, observational study
- Multicentre study
- No Randomisation
- Study duration - three weeks

**Participants**
- Age > 20 years; life expectancy estimated by a physician to be < 3 months; and incurable malignancy of abdominal origin (excluding hepatic malignancies).
- Sample size - 498 participants who met the inclusion criteria were consecutively recruited for this study.
- Exclusions - 272 participants for the following reasons:
  - 200 - death within three weeks of initial assessment,
  - 35 - survival beyond the observation period,
  - 17 - medical complications,
  - 15 - prior communication difficulty
  - 5 - discharge (n = 5).
- Final participants - 226 patients (49 from oncology units and 177 from palliative/home-care settings)

**Interventions**
- 59 - hydration group (31 from oncology and 28 from palliative/home-care settings) - those who received artificial hydration of 1 litre/day or more both one week and three weeks before death
- 167 - non-hydration group (18 from oncology and 149 from palliative/home-care settings)
- The mean hydration volume in the hydration group ranged from 838 to 1405 ml/day during the last 3 weeks, and the median hydration volume in the non-hydration group was 200 ml/day at all three observation points
- Form of hydration was unclear, but a previous paper described it as intravenous

**Outcomes**
- 1. dehydration - significantly higher in the non-hydration group (P = 0.0020).
- 2. fluid retention -
  - i) pleural effusion - significantly higher in the hydration group (P = 0.016).
  - ii) ascites - significantly higher in the hydration group (P <0.001).
  - iii) bronchial secretions - no statistically significant difference
  - iv) peripheral oedema - significantly higher in the hydration group (P = 0.039).
- 3. hyperactive delirium - no statistically significant difference
- 4. myoclonus - no statistically significant differences
- 5. bedsores - no statistically significant differences
- 6. the degree of communication capacity - no statistically significant differences
- 7. and the degree of agitation between the two groups - no statistically significant differences

**Notes**
- Rinck score 4.5

**Risk of bias**

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*Medically assisted hydration for adult palliative care patients (Review)*

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#### Viola 1997

**Methods**  
Prospective, comparative study  
Multicentre study - Edmonton (hydration group) and Ottawa (no hydration group)  
No Randomisation  
Study duration enrolment until death, no longer having a fluid deficit or discharge from palliative care unit

**Participants**  
Advanced cancer.  
Phase I - Inpatients of either Edmonton or Ottawa palliative care units with advanced cancer, not aphasic, MMSE >24 and subjectively competent (as judged by physician), able to understand English (Edmonton) or English or French (Ottawa).  
Participant at risk of developing a fluid deficit or on admission already having a fluid deficit.  
At risk was defined as history of poor oral fluid intake or excess fluid loss or both. Fluid deficit was defined as being at risk for fluid deficit (as above) plus  
a)history of decreased urine output, dry mouth sensation, thirst sensation, postural dizziness or combination or  
b) resting heart rate >100 bpm, postural drop in blood pressure 10 mm mercury or more on sitting, poor skin turgor over sternum, dry mucous membranes, enophthalmos or combination  
Exclusions: receiving enteral tube feedings, acute renal failure, pulmonary oedema or bleeding disorder, aphasic, MMSE <24  
Sample size - 288  
Excluded - 165 (164 because of cognitive deficit, one with bleeding disorder)  
Consent sought - 123  
Consented Phase I - 94  
Considered for Phase II -70  
Entered Phase II - 68 (2 excluded as no data collected) leaving 66 participants

**Interventions**  
Edmonton - 33 participants - subcutaneous fluids (titrated to participant needs) plus usual care. Solutions used were usually 0.9% saline or 0.3% saline with 3.3% dextrose. Hyaluronidase 750 units added to each one litre of fluid solution. The median volume was approximately 1000 mls/day.  
Ottawa - 33 participants - usual care

**Outcomes**  
VAS - 12 symptoms - pain, activity, nausea, depression, anxiety, drowsiness, appetite, sense of well being, dyspnoea, weakness, thirst and dry mouth. Assessed by participants or staff depending on ability of participants.  
Bowel movements  
Vomits  
Pressure ulcers  
Peripheral oedema  
Myoclonus  
Level of consciousness  
Delirium Rating scale  
MMSE
Oral mucosal assessment
Time spent in Phase II and survival from enrolment in Phase II. The demographics of the two groups differed at study entry and there were also many differences in the outcome measures at baseline. As well the results were only reported as frequency in each group, and there was no statistical analysis performed to determine if there was any significant differences between the two groups on any of the measured outcomes.

**Notes**
- Rinck score 4
- Well designed study, but the major flaw was that the two groups were not matched at study entry

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**Waller 1994**

**Methods**
- Prospective controlled.
- Single centre
- No randomisation.
- Study duration - Admission to hospice till death

**Participants**
- Palliative care patients admitted to hospice, in whom blood and urine samples were collected 48 hours or less before death

**Interventions**
- 68
- 55 hydrated orally - volumes not described
- 13 hydration - IV fluids 1 to 2 litres/day

**Outcomes**
- State of consciousness - no significant differences

**Notes**
- Rinck score = 1.5
- Methodological problems:
  - Poorly defined control group
  - No baseline data presented for groups
  - Length of time of IV fluids not included
  - Nature of IV fluid not included

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**IV** - intravenous
**bpm** - beats per minute
### Characteristics of excluded studies  [ordered by study ID]

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<th>Reason for exclusion</th>
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<tr>
<td>Morita 2002</td>
<td>Prospective controlled study that looked at fluid status of terminally ill cancer patients with intestinal obstruction. Excluded because there was no comparisons between groups with regards to hydration</td>
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<tr>
<td>Morita 2006</td>
<td>Multicenter, prospective, observational study looking at artificial hydration therapy, laboratory findings, and fluid balance in terminally ill patients with abdominal malignancies. Excluded because there was no comparison between the symptoms of the hydrated and non hydrated groups</td>
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### Characteristics of ongoing studies  [ordered by study ID]

**Bruera 2010**

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<th>A randomized, controlled trial of parenteral hydration in patients with advanced cancer</th>
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<td>Methods</td>
<td>Randomised, controlled, and double blind trial. Multicentre study</td>
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<td>Participants</td>
<td>Advanced cancer patients with decreased oral intake (&lt;=1,000 ml/day), mild to moderate dehydration, normal cognition as evidenced by the Mini Mental State Examination (MMSE) and no major contraindications to parenteral fluids are eligible. All patients are simultaneously treated by one of five hospices in the Houston area</td>
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<tr>
<td>Interventions</td>
<td>Patients are randomized into two groups: parenteral hydration (1000 ml fluids administered subcutaneously over 4 hours) versus a placebo (100 ml fluids administered subcutaneously over 4 hours)</td>
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<tr>
<td>Outcomes</td>
<td>Outcome measures include fatigue measured by the Functional Assessment of Chronic Illness (FACT-F), myoclonus, sedation, hallucinations, and delirium measured by the Memorial Delirium Assessment Scale (MDAS). The primary outcome includes the difference in symptom burden (fatigue, sedation, myoclonus, and hallucinations) between baseline and day 4. Total sample size is 150 participants; we have accrued 92 participants</td>
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DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

Date of most recent search: November 2010.
The subject search used a combination of controlled vocabulary and free text terms based on the following search strategy for searching MEDLINE:

#1 MeSH descriptor PALLIATIVE CARE explode all trees
#2 palliat* in All Text
#3 MeSH descriptor TERMINALLY ILL this term only
#4 MeSH descriptor TERMINAL CARE explode all trees
#5 (terminal* in All Text near/6 care* in All Text)
#6 ( terminal* in All Text near/6 ill* in All Text) or terminal-stage* in All Text or dying in All Text or (close in All Text near/6 death in All Text) )
#7 ( terminal* in All Text near/6 disease* in All Text)
#8 ( end in All Text near/6 life in All Text)
#9 hospice* in All Text
#10 ( end-stage next disease* in All Text or end next stage next disease* in All Text or end-stage next illness in All Text or end next stage next illness in All Text or end-stage next care in All Text or end next stage next care in All Text)
#11 ( incurable next illness* in All Text or incurable next disease* in All Text)
#12 ( advanced next directive* in All Text or living next will* in All Text or do-not-resuscitate next order* in All Text)
#13 ( advanced in All Text and disease* in All Text)
#14 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or (#9 and or #10 in All Text) or #11 or #12 or #13)
#15 MeSH descriptor FLUID THERAPY this term only
#16 MeSH descriptor DEHYDRATION this term only
#17 ( hydrat* in All Text or dehydrat* in All Text or rehydrat* in All Text or ( fluid* in All Text near/6 therap* in All Text) or ( fluid* in All Text near/6 balance* in All Text) or hypodermoclysis in All Text)
#18 (#15 or #16 or #17)
#19 (#14 and #18)

WHAT'S NEW

Last assessed as up-to-date: 13 February 2011.

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<td>14 February 2011</td>
<td>New search has been performed</td>
<td>The search for this review was re-run in February 2011. No new studies were identified to be included in this review</td>
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HISTORY
Protocol first published: Issue 4, 2006
Review first published: Issue 2, 2008

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<td>6 August 2008</td>
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CONTRIBUTIONS OF AUTHORS
PG: formulate question, write protocol, search for studies, review abstracts, retrieve studies, assess study quality, write review, update review.
MM: formulate question, review abstracts, assess study quality, critical revision of review.
JC: formulate question, critical revision of review.
PR: formulate question, critical revision of review.

DECLARATIONS OF INTEREST
None known

INDEX TERMS
Medical Subject Headings (MeSH)
Clinical Trials as Topic; Dehydration [*therapy]; Fluid Therapy [adverse effects; *methods]; Longevity; Palliative Care [*methods]; Quality of Life; Terminally Ill

MeSH check words
Humans
Chapter Four

Medically assisted nutrition for palliative care in adult patients

Chapter Four is published as:
Introduction

This chapter is a comprehensive review of available high quality studies to guide the controversial practice of medically assisted nutrition at the end of life. There were no randomised controlled studies nor prospective controlled studies identified, but this paper presented a discussion of four prospective non controlled studies and one Cochrane review.
Medically assisted nutrition for palliative care in adult patients
(Review)

Good P, Cavenagh J, Mather M, Ravenscroft P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2011, Issue 6

http://www.thecochranelibrary.com
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Medically assisted nutrition for palliative care in adult patients

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
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ABSTRACT

Background
Many palliative care patients have a reduced oral intake during their illness. The management of this can include the provision of medically assisted nutrition with the aim of prolonging the length of life of a patient, improving their quality of life, or both.

Objectives
To determine the effect of medically assisted nutrition on the quality and length of life of palliative care patients.

Search strategy
Studies were identified from searching The Cochrane Library, MEDLINE (1966 to 2008), EMBASE (1980 to 2008), CINAHL, CANCERLIT, Caredsearch, Dissertation abstracts, SCIENCE CITATION INDEX and the reference lists of all eligible trials, key textbooks, and previous systematic reviews. The date of the latest search was July 2008.

Selection criteria
All relevant randomised controlled trials (RCTs) or prospective controlled trials (if no RCTs were found).

Data collection and analysis
There were no RCTs or prospectively controlled trials found that met the inclusion criteria.

Main results
There were four prospective non-controlled trials (including one qualitative study) that studied medically assisted nutrition in palliative care participants, and one Cochrane systematic review (on Motor Neurone disease), but no RCTs or prospective controlled studies.

Authors’ conclusions
There are insufficient good quality trials to make any recommendations for practice with regards to the use of medically assisted nutrition in palliative care patients.

PLAIN LANGUAGE SUMMARY

Medically assisted nutrition for palliative care in adult patients (Review)
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Medically assisted nutrition to assist palliative care patients

It is common for palliative care patients to have reduced oral intake during their illness. Management of this condition includes discussion with the patient, family and staff involved and may include giving nutrition with medical assistance. This can be done either via a plastic tube inserted into a vein directly or into the stomach or other parts of the gastrointestinal tract. It is unknown whether this treatment helps people to feel better or live longer. A search of the international literature was only able to find a small number of studies looking at this issue. As a result, it is not possible to clearly define the benefits and harms of this treatment.

**BACKGROUND**

Many palliative care patients have a reduced oral intake during their illness. The cause of this varies, but may be part of a physical obstruction, anorexia/cachexia syndrome, generalised weakness, bowel obstruction, loss of desire to drink or no specific cause may be identified. The most common time for this decreased oral intake is during the terminal phase, when the patient becomes less conscious and therefore less able to receive nutrition orally (Morita 1998).

Management of this condition includes discussion with the patient, family and staff involved and either no medical intervention (but continued attention to treating any symptomatic problems, including good mouth care) or the provision of nutrition with medical assistance. The aim of this intervention can be to prolong the length of life of a participant, improve their quality of life, or both. These benefits may come via the reversal of the physiological factors associated with the patient’s decline. Balanced against these potential benefits are adverse events that can be associated with any intervention (infection, bleeding, pain etc) (Bozzetti 1996). It is also essential to assess the psycho-spiritual impact of undergoing the treatment and what their expectations of medically assisted nutrition are.

Medically assisted nutrition can be performed via a tube inserted into any part of the gastrointestinal system (enteral) or via a tube inserted into the venous system (parenteral). There is some controversy and views vary on the ethics of medically assisted nutrition (Casarett 2005). The first ethical controversy centres around whether medically assisted nutrition is a medical intervention or a basic provision of comfort. Secondly there is controversy as to how and by whom should decisions be made with regards to medically assisted nutrition in patients who no longer have the capacity to make decisions for themselves. This review will concentrate on assessing the benefit of provision of nutrition with medical assistance versus the harm caused by such intervention in palliative care patients. It is only with this information that clinicians and patients can make informed decisions about whether this type of intervention is beneficial or harmful to an individual patient.

A separate Cochrane review has been conducted looking at the provision of medically assisted hydration for palliative care patients (Good 2008).

**OBJECTIVES**

The objectives of this review are to determine the effect of medically assisted nutrition in palliative care patients on their quality and length of life.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All relevant randomised controlled studies (RCTs) or prospective controlled studies (if no RCTs were found).

**Types of participants**

Participants included:

- palliative care participants who received medically assisted nutrition;
- those that were receiving palliative care (WHO 2005);
- (but not be limited to) incurable cancer, dementia, neurodegenerative diseases (e.g. Motor Neuron Disease), Human Immunodeficiency Virus, Chronic Airways Limitation and Chronic Heart Failure whose prognosis was limited and the focus of care was quality of life (Doyle 2004);
- adult participants aged 18 years and above were included, both male and female and in any setting such as home, hospice or hospital.
Included participants were not limited to those in the terminal phase of their illness. Participants who were having medically assisted nutrition as part of a perioperative, chemotherapy or radiotherapy regime, or because of chemotherapy or radiotherapy adverse effects will be excluded.

**Types of interventions**

**Medically assisted administration of nutrition:**
- Parenteral nutrition - administration of nutritional liquid via a central or peripheral venous catheter, that does not directly enter the gastrointestinal system;
- Enteral nutrition - administration of nutritional liquid through a tube via the gastrointestinal system (nasogastric tube, jejunostomy, gastrostomy).

**Comparisons:**
- Placebo,
- No intervention,
- Usual treatment or supportive care.

**Types of outcome measures**

**Primary outcomes**
1. Quality of life on any measure (including symptom assessment scales)

**Secondary outcomes**
1. Survival
2. Adverse Events

**Search methods for identification of studies**

**A. Electronic Databases**
The following electronic databases were searched using a search strategy developed for MEDLINE, but modified appropriately for each database:
- The Cochrane Library: Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Cochrane Database of Reviews of Effectiveness.
- MEDLINE (1966 to present).
- EMBASE (1980 to present).
- CINAHL.
- CANCERLIT.

- Caresearch - database listing conference proceedings and grey literature.
- Dissertation abstracts.
- SCIENCE CITATION INDEX.

Date of most recent search: July 2008

**B. Reference Lists**
The reference lists of all eligible trials, key textbooks, and previous systematic reviews were searched for additional studies.

**C. Language**
The search attempted to identify all relevant studies irrespective of language. There were no non-English papers identified. The subject search used a combination of controlled vocabulary and free text terms based on the search strategy for searching MEDLINE. Please see Appendix 1.
This search strategy was adapted for other databases searched.

**Data collection and analysis**
Studies identified by the search strategy had the title and abstract (where possible) assessed by the lead review author (PG) to identify potentially relevant articles.
The results of studies identified from the different databases were as follows:
The Cochrane Library - 1136 (476 from clinical trials)
MEDLINE - 6655
EMBASE - 4548
CINAHL - 56
CANCERLIT - 2480
Caresearch - 172
Dissertation abstracts - 54
SCIENCE CITATION INDEX - 4601
After review of the title and abstracts, 22 references were retrieved in full. Unfortunately none of these met the inclusion criteria. However, there were four prospective non-controlled trials (including one qualitative study), and a Cochrane systematic review. These studies will be described in the discussion section.

**Quality**
All studies were to have their methodological quality assessed. There was to be two scales used.
1. RCTs would be assessed via the Oxford Quality Scale devised by Jadad et al (Jadad 1996).
2. The quality of non RCTs would be assessed using a scale devised by Rinck et al (Rinck 1997).
Data extraction
The following information was planned to be obtained for each study:
- study methods (study design, allocation, blinding, setting, inclusion criteria);
- participants (sample size, exclusions/inclusions, number, disease, duration of trial, withdrawals and dropouts, site - e.g. hospital, hospice, home);
- intervention (type, route of delivery, control used);
- outcome (quality of life, symptom measures, survival, time from death intervention was initiated);
- adverse effects.

The extraction was to occur independently by two review authors.

Data analysis
The overall effectiveness of medically assisted nutrition in palliative care participants was to be assessed and also specific sub-group analysis (where possible) was to be undertaken by:

- study design:
- data from RCTs and prospective controlled studies were to be evaluated separately
- participants:
  - cancer,
  - non-cancer,
  - dementia,
- intervention:
  - medically assisted nutrition - parenteral, enteral nutrition.
- study quality
- timing of intervention (in relation to death)
- site

Risk of bias in included studies
No studies were evaluated for methodological quality.

Effects of interventions
There were no RCT nor prospectively controlled trials found that met the inclusion criteria.

DISCUSSION
The objective of this systematic review was to determine the effectiveness of medically assisted nutrition in palliative care patients (of all ages) on their quality and length of life. Extensive searching of the literature produced no RCTs nor prospective controlled trials that fulfilled the inclusion criteria. The discussion will focus only on prospective trials that were retrieved, as this represents the next highest study quality design. However, the studies are all of a low quality because of their design, and therefore caution is needed in interpreting any of the results.

Statistical analysis
No studies were suitable for evaluation.

RESULTS
Description of studies
See: Characteristics of excluded studies.
No studies met the inclusion criteria.

Excluded studies
Please see Table 1 in 'Additional tables' and the Characteristics of excluded studies table.

This search identified four prospective non-controlled trials (including one qualitative study) that studied medically assisted nutrition in palliative care participants (Bozzetti 2002; Meier 2001; Orrevall 2005; Pironi 1997), and one Cochrane systematic review (Langmore 2006). One study (Meier 2001) included participants with advanced dementia. The other three studies (Bozzetti 2002; Orrevall 2005; Pironi 1997) included only participants with advanced cancer. In two studies (Bozzetti 2002; Orrevall 2005) participants received only parenteral nutrition, whilst in another two studies (Langmore 2006; Meier 2001) the included participants had enteral nutrition. In one study (Pironi 1997) included participants had either enteral or parenteral nutrition. The Cochrane review (Langmore 2006) assessed participants with motor neuron disease.

Survival was measured in three studies (Bozzetti 2002; Meier 2001; Pironi 1997) and evaluated in the systematic review (Langmore 2006). Quality of Life (QOL) was used as an outcome measure in three of the studies (Bozzetti 2002; Langmore 2006; Orrevall 2005). Two studies look at the effect of the intervention on Karnofsky Performance Scale (KPS) (Bozzetti 2002; Pironi 1997). Only
one study recorded adverse events of the interventions (Pironi 1997). The qualitative study analysed the positive and negative features according to the themes derived from the data (Orrevall 2005).

In a prospective, cohort study of participants with advanced dementia there was no significant difference, in survival, between those participants with PEG inserted (median 195 days, range 21 to 1405 days), and those without PEG insertion (median 189 days, range four to 1502) (P = 0.9) (Meier 2001). The Cochrane review had conflicting results, in that three studies found a longer survival in participants who had a PEG, whilst the other four studies found no difference. Bozzetti 2002 found that participants on home parenteral nutrition (HPN) had a median survival of four months. The mean survival was used when Pironi 1997 looked at participants on HPN (12.2 weeks) and those on home enteral nutrition (17.2 weeks). QOL did not improve after PEG insertion for participants with motor neuron disease (Langmore 2006), nor at one month in those with advanced cancer (Bozzetti 2002), but there was a perceived benefit in this area in the qualitative study (Orrevall 2005). In one study (Bozzetti 2002) the KPS was stable until a progressive decline at three months prior to death, whilst another study (Pironi 1997) found that at one month after intervention the KPS was increased in 13 participants, decreased in 19 participants, and was unchanged in 132 participants. The qualitative study of advanced cancer participants in Sweden (Orrevall 2005) found that HPN produced positive features including assurance that nutrition was being met, and this led to a perceived benefit on energy, strength and activity. It was also seen as decreasing the feeling of “pressure to eat” and more acceptance of whatever was able to be eaten orally.

Pironi 1997 found that with HEN, there was NG tube blockage/dislodgment in 0.26 per year of HEN and PEG site infection in one participant and hub replacement in two participants, whilst the complications of treatment with HPN (per year of treatment were catheter sepsis (0.67), DVT (0.16) and metabolic instability (0.50). This study also attempted to look at the burden of medically assisted nutrition for participants and their families. However, this was only done as a judgement by nutrition staff, and was therefore open to a large element of bias. They found that medically assisted nutrition was well accepted in 124 cases (19 HPN), with annoyance in 30 cases (seven HPN), and scarcely tolerated in ten cases (three HPN). The qualitative study (Orrevall 2005) found that the negative features of HPN were related to physical symptoms of nausea, vomiting, drowsiness and headache, as well as HPN placing a restriction on their family life and social involvement.

**Implications for practice**

There are insufficient good quality studies to make any recommendations for practice with regards to the use of medically assisted nutrition in palliative care patients. Clinicians will need to make a decision based on the perceived benefits and harms of medically assisted nutrition in individual patient circumstances, without the benefit of high quality evidence to guide them. The uncontrolled prospective studies described would suggest that patients with a good performance status and medium to long term prognosis (months to years) may benefit from medically assisted nutrition. However, the evidence base to support this at the moment is weak and any intention to use this treatment should be monitored carefully and ideally fed in to further research.

**Implications for research**

**Trial design**

There are very few quality studies that have looked at the question of medically assisted nutrition in palliative care patients. It may be difficult to ever do a RCT in this area. The logistics of recruiting participants to any palliative care trial are well known (Rinck 1997) but are especially so with regards to medically assisted nutrition. There are two distinct palliative care populations, in which further trials of the effect of medically assisted nutrition would be useful. The first is those patients who develop the anorexia/cachexia syndrome. The second is in those patients who are unable to swallow, but whose prognosis (from their cancer) would seem to be longer than their prognosis from the aphagia. The difficulty in this situation is the reliance on the physicians ability to provide a prognosis, and this is not always accurate (Glare 2003).

As well as looking at the possibility of RCTs in this area, the evidence base will be improved with at least some prospective controlled trials, and even with more prospective uncontrolled trials. This may need to be done with innovative designs such as comparisons between different centres that have different nutrition practices or by following up cohorts of participants who are offered medically assisted nutrition, in whom some proceed and some do not (as long as the two groups are similar).

**Patient groups**

The studies in this review did not have well defined patient populations. Palliative care is performed in hospital, in-patient palliative care units and the community. Trials need to be performed in all these areas to allow external validity (able to be applied to a similar patients as those seen in a trial) to different palliative care populations. It would also be helpful to define at what stage of their illness participants are being given medically assisted nutrition. The reasons and aims of nutrition in the last few days/weeks of life may be very different to those participants with a longer prognosis. The prospective prediction of prognosis is difficult, and

**Authors' conclusions**

Medically assisted nutrition for palliative care in adult patients (Review)

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it may be better to stratify participants according to performance status.

Interventions
Medically administered nutrition can be given by many different routes. Further trials are needed to determine the optimum route and dose.

Outcomes
It is important that clinically relevant outcomes are clearly defined and are the most clinically useful to this situation. In this patient population this includes energy levels, functional status and overall quality of life. As well as these, the effect of this intervention on overall survival needs to be reported. Also important is that adverse events are well defined so that the risk of treatment can be balanced against any benefits.

REFERENCES

References to studies excluded from this review

Bozetti 2002  {published data only}

Langmore 2006  {published data only}

Meier 2001  {published data only}

Orrevall 2005  {published data only}

Pironi 1997  {published data only}

Additional references

Bozetti 1996

Cassaret 2005

Doyle 2004

Glare 2003

Good 2008

Jadad 1996

Morita 1998

WHO 2005

* Indicates the major publication for the study
## Characteristics of Studies

**Characteristics of excluded studies**  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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</thead>
<tbody>
<tr>
<td>Bozzetti 2002</td>
<td>Prospective non-controlled trial.</td>
</tr>
<tr>
<td>Langmore 2006</td>
<td>Retrospective case control studies, and prospective cohort studies</td>
</tr>
<tr>
<td>Meier 2001</td>
<td>Prospective non-controlled trial.</td>
</tr>
<tr>
<td>Orrevall 2005</td>
<td>Prospective non-controlled trial.</td>
</tr>
<tr>
<td>Pironi 1997</td>
<td>Prospective non-controlled trial.</td>
</tr>
</tbody>
</table>
DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Data on excluded studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozzetti 2002</td>
<td>Prospective, observational study</td>
<td>69 adult cancer participants</td>
<td>HPN External tunnled catheters (51 participants) and porta cath (18 participants)</td>
<td>Median survival was four months, after participants began HPN At one month there was no significant change from baseline with regards to Quality of Life (using Rotterdam symptom checklist) with 40% improved, 50% deteriorated and 10% no change). The Karnofsky Performance Status (KPS) was stable until progressive decline at three months prior to death</td>
<td></td>
</tr>
<tr>
<td>Langmore 2006</td>
<td>Cochrane systematic review</td>
<td>Motor neuron disease</td>
<td>Medically Assisted Nutrition (via enteral tube feeding)</td>
<td>There were no RCTs found. The review discussed seven studies. Five of these studies were retrospective case controlled. Two were prospective cohort studies (Chio 2002 and Mazzini 1995). All seven studies tested for survival advantage of intervention. Three found a longer survival in participants who had a PEG, whilst the other four found no difference.</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Data on excluded studies (Continued)

<table>
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<tr>
<th>Study</th>
<th>Data on Excluded Studies</th>
<th>Only three studies looked at nutritional outcomes and these suggested a positive advantage for those participants with PEGs. Only two studies looked at QOL, and both failed to show improvement in QOL after PEG insertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier 2001</td>
<td>Prospective, cohort study. This was part of a study looking at increased consultation versus usual care in the management of participants with advanced dementia. 182 eligible participants - 99 consented to inclusion in study. The ninety three participants were excluded because of: - no available surrogate decision maker (40), - surrogate decision maker unable to understand and participate in informed consent (19), - surrogate decision maker refused informed consent (five), - subject imminently dying or medically unstable (eight), - language barrier (three), family conflict (three), and - transferred/discharged/died (five). The participants had been admitted to a New York hospital with an acute illness (Pneumonia or Urinary Tract Infection (61), dehydration or metabolic abnormality (12), Other (26)). Of the 99 study participants, 82 had no feeding tube on admission (two admitted for insertion of feeding tube). Of these 82 participants, 51 had a PEG inserted during the index admission. The median survival was not significantly different between those participants with PEG inserted (median 195 days, range 21 to 1405 days), and those without PEG insertion (median 189 days, range four to 1502) (P = 0.9)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Methodology</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Orrevall 2005</td>
<td>Qualitative</td>
<td>13 participants were interviewed and 11 family members, during 2000 to 2001, in Sweden. These were recruited via advanced home care teams (AHCT) nurses being asked to contact participants with advanced cancer. Participants contacted were asked to provide names of relatives who were also willing to participate. Nine participants received partial HPN and oral intake, two were on total HPN and two were actually weaned from HPN. The intervention consisted of HPN for at least two weeks (and at least three times per week), with an AHCT nurse connecting and disconnecting the infusion each time. Ten of the participants died within six months of the interview, but eleven lived greater than three months. The positive features (according to participants and relatives) included assurance that nutrition was being met, and this led to a perceived benefit on Quality of life, energy, strength and activity. It was also seen as decreasing the feeling of &quot;pressure to eat&quot; and more acceptance of whatever was able to be eaten orally. The benefits of HPN were very much related to the close involvement and frequent visits of the AHCT nurses. The negative features of HPN were related to physical symptoms of nausea, vomiting, drowsiness and headache. As well HPN placed a restriction on the family life and social involvement.</td>
</tr>
<tr>
<td>Pironi 1997</td>
<td>Prospective</td>
<td>Italian advanced cancer patients. Participants were described as having advanced cancer when receiving only palliative care. Participants were included if they had hypophagia (oral calorie intake absent or &lt;50% of basal energy expenditure (Harris-Benedict formula), life expectancy greater than six months. The method of intervention for 135 participants with HEN was using a nasogastric tube (50%), percutaneous endoscopic gastrostomy (18%), jejunostomy (27%), and surgical gastrostomy (5%). The infusion method was pump (83%) and via gravity (17%). In the 29 participants Mean survival was 17.2 weeks for participants on HEN and 12.2 weeks for participants on HPN. This included 47 participants (29%) who survived less than six weeks. This was most common in groups with the primary tumour outside gastrointestinal tract and head-neck.</td>
</tr>
</tbody>
</table>
Table 1. Data on excluded studies (Continued)

| Region and in the group with a Karnofsky Performance Score (KPS) of less than or equal to 40. During the first month of HAN the KPS increased in 13 participants, decreased in 19 participants, and was unchanged in 132 participants. Twelve participants on HEN became able to go out and look after themselves unaided, whilst two became housebound. Body weight increased in 43 participants, decreased in 21 participants and there was no change in 80 participants, with 20 participants confined to bed and unable to be weighed. Of the 108 participants excluded because their estimated survival was less than six weeks, 31 (29%) lived greater than or equal to six weeks. During treatment there were 95 participants (61%) who underwent 155 hospital readmissions. This included three admissions for HPN complications and seven for jejunostomy po-
An attempt was made to record the burden to the participant and families. This was judged by the nutrition staff, and was dependent on the level of complaints of the participant and families. They found that HAN was well accepted in 124 cases (19 HPN), with annoyance in 30 cases (seven HPN), and scarcely tolerated in ten cases (three HPN).

In terms of complications with HEN, there was NG tube blockage/dislodgment in 0.26 per year of HEN and PEG site infection in one participant and hub replacement in two participants. The complications of treatment with HPN (per year of treatment were catheter sepsis (0.67), DVT (0.16) and metabolic instability (0.50)
APPENDICES

Appendix I. Search strategy

#1 MeSH descriptor PALLIATIVE CARE explode all trees
#2 palliat* in All Text
#3 MeSH descriptor TERMINALLY ILL this term only
#4 MeSH descriptor TERMINAL CARE explode all trees
#5 (terminal* in All Text near/6 care* in All Text)
#6 (terminal* in All Text near/6 ill* in All Text) or terminal-stage* in All Text or dying in All Text or (close in All Text near/6 death in All Text)
#7 (terminal* in All Text near/6 disea* in All Text)
#8 (end in All Text near/5 life in All Text)
#9 hospice* in All Text
#10 (end-stage next disease* in All Text or end next stage next disease* in All Text or end-stage next illness in All Text or end next stage
next illness in All Text or end-stage next care in All Text or end next stage next care in All Text)
#11 incurable next illness* in All Text
#12 incurable next disease* in All Text
#13 (advanced next directive* in All Text or living next will* in All Text or do-not-resuscitate next order* in All Text)
#14 (end-stage next disease* in All Text or end next stage next disease* in All Text or end-stage next illness in All Text or end next stage
next illness in All Text or end-stage next care in All Text or end next stage next care in All Text)
#15 (advanced in All Text near/6 disease* in All Text)
#16 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
#17 MeSH descriptor NUTRITION explode all trees
#18 MeSH descriptor NUTRITION ASSESSMENT explode all trees
#19 MeSH descriptor NUTRITION THERAPY explode all trees
#20 MeSH descriptor FEEDING METHODS explode all trees
#21 (feed in All Text or feeding in All Text or fed* in All Text or food* in All Text)
#22 MeSH descriptor FOOD explode all trees
#23 diet* in All Text
#24 nutrition* in Record Title
#25 nutrition* in Abstract
#26 (#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#27 (#16 and #26)

WHAT’S NEW

Last assessed as up-to-date: 17 July 2008.

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<td>Amended</td>
<td>Contact details updated.</td>
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HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2008

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<tr>
<td>30 October 2008</td>
<td>Amended</td>
<td>Minor edits made to text using new RevMan 5 software</td>
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CONTRIBUTIONS OF AUTHORS

Phillip Good: formulate question, write protocol, search for studies, review abstracts, retrieve articles, assess article quality, write review, write update.

John Cavenagh: formulate question, critical revision of review.

Peter Ravenscroft: formulate question, critical revision of review.

Mark Mather: formulate question, critical revision of review.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

- *Enteral Nutrition [adverse effects; methods]
- *Parenteral Nutrition [adverse effects; methods]
- Longevity
- Palliative Care [*methods]
- Quality of Life

MeSH check words

Adult; Humans
Chapter Five

Palliative care professionals' perceptions of nutrition and hydration at the end of life

Chapter Five is published as:
This interest in nutrition and hydration at the end of life led to further studies using a qualitative methodology. This chapter is a qualitative study, published in a prominent nursing journal, that was the first to look at how Palliative Care clinicians in different settings perceive a complex medical and ethical dilemma. It found that Palliative Care clinicians believe that MANH rarely benefits patients, but recognise the emotional distress that family members experience in dealing with this situation.
Abstract
The provision of medically administered nutrition and hydration (MNH) for the terminally ill patient is a controversial issue and there has been much debate in the literature concerning this sensitive subject. This article reports on a qualitative research study that explores palliative care nurses' and doctors' perceptions and attitudes to patient nutrition and hydration at the end of life. Participants were from an urban and rural palliative care service. Three main discourses were identified: carers’ distress at the non-provision of MNH; palliative care doctors’ and nurses’ position that terminal dehydration lessened the burden of suffering for dying patients; and polarisation between the acute care setting and the palliative care setting. Overlaying these three main discourses are contesting discourses involving cure vs comfort, and acute care vs palliative care. Importantly, the findings of this study reveal that palliative doctors and nurses believe that medically assisted nutrition and hydration at the end stage of life rarely benefits patients, and as long as adequate mouth care is given, patients do not suffer. However, family members do experience emotional distress in dealing with this situation. In caring for dying people, the nurse’s and doctor’s role is one of education and communication, involving a team approach to manage this difficult issue.

Management of decreased oral intake includes communication between the patient, family and staff involved and either the provision or non-provision of MNH. Medically assisted nutrition (MAN) can be performed enterally (insertion of tube into any part of the gastrointestinal system) or parenterally (use of the venous system), while medically assisted hydration (MAH) is usually performed parenterally (via the intravenous or subcutaneous routes). It is important to realize that MAN and MAH are two very different and usually separately approached treatments. The aim of MNH can be to prolong the length of life of a patient, improve their quality of life, or both. These aims may be achieved if there is a reversal of the physiological factors associated with the patient’s deterioration. However, as with any medical intervention there is potential to cause adverse effects as well (Bozzetti, 1996).

There are few high-quality prospectively controlled studies looking at the benefits and adverse effects of the provision of MNH (Table 1).

Hydration
Waller (1994) performed a prospective, controlled study on 68 palliative care patients in a hospice setting. This study looked at the effect of intravenous fluids (1–2 litres/day) in 13 patients compared to 55 patients who were hydrated orally. The main symptomatic outcome was level of consciousness and there was no significant difference found between the two groups.

Cercietti et al (2000) undertook a randomized, controlled trial in terminal stage advanced cancer patients. Forty-two patients were included who could not maintain an adequate water intake (less than 50 ml/day). Twenty-two patients were given 1 000 ml/day of subcutaneous fluids, while the other 22
continued with usual treatment. The primary outcome measures were thirst, chronic nausea, delirium and mini mental state examination (MMSE) with secondary outcome measures of anguish, mood, interruption of hydration and local adverse reactions. The authors stated that, ‘1 000 ml/day subcutaneous hydration does not improve control of the assessed symptoms when added to the general and pharmacological treatment in patients with end-stage cancer. However, control of chronic nausea after 24 hours was significantly better in the group receiving hydration.’

A prospective, observational study of the effect of hydration in 226 patients with advanced abdominal malignancies was performed in Japan (Morita, 2005). Fifty-nine patients received hydration (1 litre/day or more) and they were compared to 167 patients who received no medically assisted hydration. There was no difference found between the groups in terms of hyperactive delirium, myoclonus, bedsores, agitation, communication capacity or bronchial secretions. Pleural effusion, peripheral oedema and ascites were higher in the hydration group, while dehydration was higher in the non-hydration group.

In the USA, Bruera et al (2005) undertook a randomised, controlled, double blind trial looking at the effect of parenteral hydration on 51 patients with advanced cancer and an oral intake of less than 1 000 ml per day and evidence of mild-to-moderate dehydration. Twenty-eight patients were given 1 000 ml normal saline as an infusion over four hours for two days, and 23 received placebo (100 ml normal saline as an infusion over four hours for two days). The main outcome was the global assessment of the overall benefit of hydration to the patient, as determined by the physician and patient on Day 2 and there was no statistically significant difference between the two groups. Individual symptoms were also recorded and there was found to be no difference between the groups with regard to fatigue, hallucinations and MMSE. However, there was improvement in the hydration group in relation to sedation and myoclonus.

The results from these studies suggest that there may be some benefit, from hydration, in terms of improvement in sedation and myoclonus, but that there may be some harm in terms of worsening of fluid retention symptoms (pleural effusion, peripheral oedema and ascites).

There have been no good-quality prospective controlled studies examining MAN in palliative care patients. Some uncontrolled prospective studies would suggest that patients with a good performance status and medium-to-long-term prognosis (months to years) may benefit from MAN, but the evidence base to support this is very weak (Pironi, 1997, Meier; 2001; Bozzetti, 2002; Orrevall, 2005; Langmore, 2006).

The provision of MNH for the terminally ill patient is a controversial issue and there has been much debate in the literature concerning this sensitive subject (McCann et al, 1994; Fainsinger and Bruera, 1997; Smith, 1997; Lanuke and Fainsinger, 2003). It is not uncommon for health care professionals, such as nurses and doctors, to be nervous about discontinuing nutrition and hydration for the patient at the end stage of life (van der Riet et al, 2006). Family members may ask for MNH because they fear that their family member is ‘starving to death or suffering with thirst’ and health care professionals can occasionally be viewed as complicit in the patient’s death (van der Riet et al, 2006).

In palliative care practice, the provision of MNH may occur for selected patients during the course of their illness, but it is rarely provided during the terminal phase. In palliative care units, food and drink, and assistance with eating and drinking, are always available to satisfy a patient’s thirst and hunger, but medical means are not routinely used when oral intake ceases (Huffman, 2000).
A recent study undertaken by van der Riet et al (2006) interviewed five terminally ill inpatients and five family members. These patients had their food and fluid intake monitored until they died (van der Riet et al, 2006). Their findings revealed that these patients were neither hungry nor thirsty, and that there was not the dramatic cessation of fluid and food with ill effects of starvation, but instead a gentle reduction of fluid and food (van der Riet et al, 2006). However, this palliative care experience is not widely known among health professionals or the wider community (McAulay, 2001; Ashby and Mendelson, 2003). Even within the medical profession there has been disagreement regarding the provision of MNH for terminally ill patients (Fainsinger and Bruera, 1997; Huffman, 2002).

Our interest in fluid and nutrition at the end of life stemmed from our experiences while working in palliative care, and our increasing concern over family members wanting to feed patients when they were clearly unable to eat or drink. From the authors’ experiences this was an issue that was often raised and discussed at family meetings in the palliative care units in which we had worked.

This research examines these issues with health professionals. The study documents the experience of doctors and nurses working in palliative care dealing with the provision and non-provision of MNH in terminally ill patients.

**Setting of the study**

The setting for the study was two palliative care units in New South Wales, Australia. One unit is a tertiary referral service for about 800,000 patients and has a 20-bed inpatient unit. There are approximately 400 inpatient deaths per year, and about 225 patients on the palliative care nursing service at any one time. The median time from referral to the programme to death is 54 days (Good et al, 2004). The other unit is in a major rural hospital and has a ten-bed ward in which both general medical patients and palliative care patients are admitted. In the palliative care nursing service, there are 74 patients at any time and there are about 108 deaths per year within the service.

**Ethical aspects of the research**

Before collecting data for this study, an ethics proposal was reviewed and approved by the Human Research Ethics committee at the University and by the area health service. Confidentiality of all information was assured to all participants via the consent form and information statements distributed. All data were treated as strictly confidential and pseudonyms have been used in this paper. Focus group and interview participants were requested to maintain the confidentiality of the group discussion and not divulge the specific content of such discussion to outside parties. Any names or identifying information recorded were omitted as the recording was transcribed.

**Method and methodology**

Once the authors had received ethics approval from their organisation, recruitment of participants began. Data were collected over a six-month period with two focus group interviews involving 15 nurses working in two separate palliative care units and four single interviews with doctors from the tertiary palliative care unit. Single interviews with doctors were chosen to allow for greater flexibility of access.

The technique of discourse analysis has been used to analyse the data generated in this study. Discourse analysis is a widely used qualitative technique that has been adopted within public health, sociology, psychology, education, linguistics and communication. However, in the literature there are lots of different interpretations as to how to carry out discourse analysis. We recommend particular attention be paid to the language used by the participants, focusing on the metaphors, euphemistic expressions, pronouns, and binaries and subject positions. O’Connor and Payne (2006) state that discourse analysis ‘has the potential to contribute to new ways of seeing palliative care practices by a deconstruction of meanings.’ Discourses provide subject positions which constitute subjectivities in particular ways. In this research we aimed to explore how palliative care nurses and doctors construct a position on fluid and nutrition at the end of life. Discourse analysis provides a lens to examine the perceptions of our participants. Furthermore, it is important to explore the discourses and see if they make sense and if they are contesting. Throughout this paper there are several underlying contesting discourses involving cure vs comfort and acute care vs palliative care. Themes (such as burden of suffering and hope and technology)
within discourses were identified and gave insight into how staff perceive, construct and communicate issues of nutrition and hydration at the end stage of life, and, therefore, how this might impact on their work with patients and families.

Discourse analysis allows the researcher to develop an understanding of the participant’s experience. Meanings from talk and text which may not necessarily be visible are revealed (O’Connor and Pearson, 2004). In this paper we have used Foucault’s definition of discourse involving deep principles and grids of meaning that underpin people’s ways of thinking and doing (Drefus and Rabinow, 1982). In discourse analysis one ‘seeks to understand the rules, mechanisms and structure of conversations’ (Polit and Beck, 2005). Meanings from talk and text which may not necessarily be visible are revealed (O’Connor and Pearson, 2004).

Once data had been collected, the following steps adapted from Gill’s (2000) discourse analysis were used.

- Data were read and interrogated and this involved interrogating researchers’ own assumptions and the ways they made sense of realities.
- Data were coded as inclusively as possible.
- The research question was revised as patterns in the data emerged.
- Data were analysed by examining regularity and variability in the data.
- In addition to Gill’s steps, data were analysed for contesting discourses and explored for subject positions, binaries and metaphors.

**Discussion and findings**

Analysis of the data revealed three main discourses:

- Carer’s distress at the non-provision of MNH
- Palliative care doctors’ and nurses’ position that terminal dehydration lessened the burden of suffering for dying patients
- Polarisation, with differences in the acute care setting and in the palliative care setting.

**Carers’ distress at the non-provision of MNH**

Feeding and hydration linked to compassion and nurturing

In this study, fluids and food were seen by family members as more than just treatment, and were connected to comfort and care. Feeding and hydration were linked to compassion and nurturing. For example, as one doctor comments:

‘Many patients and families really feel that feeding and fluids are more than just treatment, they’re about comfort and care and so because families have a concern about it, I’m concerned about it as well.’

Families were often reported as distressed over the non-provision of fluid and nutrition at the end stage of life, seeing it as contributing to deterioration of the patient. As one participant doctor reported:

‘People sort of have the picture of dehydration (that it) is like someone in the desert.’

This metaphor of someone in the desert positions dehydration as one of abject suffering and entrapment with no escape. The image of thirst and suffering is very powerful here.

A common feature of a family’s response to the perception of their loved one is guilt. Nursing staff and doctors interviewed in this study all recommended that families needed better communication, rather than be left to deal with this issue themselves.

**Hope and technology**

Hope and technology were linked in that technology gave families hope that something was being done for their loved ones. Hope is often used in discursive ways, for example, against death, and it is used actively against giving up. One participant doctor states:

‘I guess for most patients all of that interventional stuff means hope, and then we come to the stage when we don’t give them IV fluids or whatever and these are all confronting steps and acknowledgement that the path to cure is gone. And I think you know it’s important to, aside from the medical issues, to look at the symbolism for the family.’

In not providing medical nutrition and hydration there is a perception that the family and patient are being abandoned and hope has been taken away. This is consistent with a recent palliative care study that reported that when active treatment ceased, patients and families perceived that hope had been taken from them (Thompson et
al, 2006). Evident here is another competing discourse of acute care vs palliative care and overlaying this is another competing discourse of cure vs comfort.

This symbolism for the family is about food being linked to compassion and nurturing. Food gives life and the provision of medical nutrition and fluids helps provide life and hope. This is supported by van der Riet et al’s (2006) study which showed that ‘food was seen as symbolic of life and also of ‘not letting go’. This study reported that family members would bring in special treats for their loved one in the belief that it would give dying patients more energy. Feeding the patient made them feel useful, however, it contained their grief and also helped deny it (van der Riet et al, 2006).

The professional’s position that terminal dehydration lessens the burden of suffering for dying patients

Here, we see competing discourses between doctors and nurses and family members. Contrary to what family members, and the general community, believe about the issues in this study, dehydration was reported by doctors and nurses to be a normal part of the dying process with patients not experiencing any suffering or thirst. Examples of this are supported by the following doctor’s comments:

‘Dehydration is a normal part of the dying process and so therefore, to interfere with that tends to create more suffering.’

Burden of suffering

All the participants in this study commented that medical hydration may contribute to a burden of suffering for dying patients. In relation to the physiology of the illness, dying patients are not hungry and this participant (doctor) would advise the family members:

‘With regard to food, I tell them that very often the cancer secretes hormones which really turn the appetite off and in that situation, it’s not that we’re not feeding them, it’s that the patient doesn’t feel like eating and the policy of the Hospice here is to offer everyone food, and it’s their option whether or not they take it.’

The importance of communication, and educating family members about the changes that occur when a person is dying becomes an important part of patient care.

Freedom from attachment/tubes, freedom from burden of suffering

Medical hydration for dying patients was seen as invasive and was not in line with the palliative care ethos of comfort. A number of participants in this study commented that the attachment of tubes contributed to the burden of suffering. The freedom from attachments such as tubes made communication easier.

Some nurses reported that technology took away from intimacy and communication. A nurse comments on the intrusiveness of technology and the potential for technology to interfere with emotional contact:

‘I think your opportunity for physical and emotional closeness increases when extra equipment and tubes and things are taken away so that there’s just the person and his carer there, without external devices. I think that then facilitates the emotional and physical closeness to increase.’

Mouth care to reduce the burden of suffering

A dry mouth was sometimes an issue; however, palliative care staff did not see this as adding to the burden of suffering, providing good mouth care was given. In van der Riet et al’s (2006) research, thirst was not a problem, provided that good mouth care was given regularly. Thirst was rarely seen to be an issue and if experienced could also be alleviated. The following participant (doctor) offers the following strategies to alleviate dry mouths and thirst:

‘Very often, the thirst is a sensation around the mouth, and lips and tongue, and that can be palliated with you know, good oral care, strategies, salivary stimulations, salivary production like you know cold chunks of pineapple.’

Another doctor commented on the importance of good communication and giving family a sense of control in relation to mouth care:

‘We’re very much into explaining to the families that dehydration is not always associated with dry mouth and all that, and excellent mouth care and so on can be a very good way of managing that and often the family can be involved in moistening the mouth and so on which again gives them some control over
Meticulous mouth care involves not just swabbing the mouth, but regularly removing debris from the mouth with water and peroxide rinses, brushing gums, teeth and tongue with a soft toothbrush or sponge (Zerwekh, 1997).

Communication and open discussion with families
Threaded throughout the findings in this study has been the importance of communication, especially that which will lessen families’ distress. The importance of listening is evident in the following nurse’s talk:

‘You’d sit down and listen to them and what they’re feeling…and initially it’s a fear and just find out what they’re really fearful of and I guess educate them in various informative ways and, sometimes you can go along with their wishes but then you need to back off very slowly. I think it depends on the family.’

Polarization with differences in the acute care setting and the palliative care setting
Throughout the interviews there was evidence of a polarization between the palliative care and acute care ethos and, therefore, a contesting discourse of acute care vs palliative care. The palliative care ethos was one of promoting comfort and quality of life, whereas the acute care approach to managing dying patients involved the medical provision of fluids and was one of technology and invasiveness. The following nurse comments that young doctors need to be educated about the palliative care ethos:

‘My experience was that (with) a lot of young doctors who came from acute care to work in the palliative care unit you have to spend more time re-educating them. You know, they go for the cannula.’

Furthermore, a doctor reports:

‘It can be difficult the withdrawal of hydration, especially hydration in some settings can be more difficult – we can only ever advise what we would do in that setting and if we are asked to consult a patient, we go and talk to the patient about our perspective on these things… but when they are under the care of another team of course we can not push our own agenda too much we can only give an option without saying this is the be all and end all.’

The transition from acute care treatment to palliative care has been identified as a difficult process and often fraught with much uncertainty involving the blurring of boundaries of curative and palliative care (Thompson et al, 2006).

Study limitations
The findings in this study reflect the views of the staff of only two palliative care services. In addition, the findings may not be generalisable to palliative care provided in acute hospital settings, nor other countries. There may be other views such that a bigger study involving other palliative care units might show up different discourses. The doctors in these interviews tended to be more expansive in their responses than did the nurses. This could be explained by the nature and context of the focus group in that doctors were able to respond to the interviewer on a one-to-one basis, whereas nurses were interviewed in focus groups of seven to eight people in each interview. The environment of the single interviews with doctors was quiet, whereas at times the focus groups were noisy and chaotic with some participants more vocal than others. Crowe (2005) points out that the context in which the research data are collected constructs the characteristics of data and in discourse analysis one cannot separate the data from the context. This in itself could be a limitation because the noisy environment of focus groups precludes some participants from in-depth talk. Within the nurse focus group interviews it was often noted that a small number of nurses spoke for the group and others agreed with these responses. That is, a few nurses appeared to articulate the thoughts of others. However, there was consistency among the nurses’ ideas in the focus groups.

Conclusion/summary
The findings of this study reveal numerous contesting discourses between health professionals and family members involving cure vs comfort and acute care vs palliative care. Palliative doctors and nurses believe that medically assisted nutrition and hydration at the end stage of life rarely benefit patients, and as long as adequate mouth care is given, patients do not suffer. However, family members do experience emotional
Palliative care professionals’ perceptions of nutrition and hydration at the end of life

distress in dealing with this situation. We recommend that in caring for dying people the nurse’s and doctor’s role is one of education and communication, involving a team approach to manage this difficult issue. We also suggest exploring this research further in acute care, including paediatrics and in the aged care setting. There is a strong case to argue that staff in different health care settings need more information and knowledge about the difference between the pathophysiology of dying (dehydration, malnutrition) and the symptoms people are worried about (hunger, thirst) as these are usually unrelated, but often perceived to be the same. We recommend developing clinical guidelines so that there is consistency in how the issues of terminal dehydration are managed for dying patients.


Key words
- Nutrition
- Hydration
- Palliative care
- Dying
- Dehydration

Van der Riet P, Higgins J, Good P, Sneeby M (2007) Does the provision and non provision of medical nutrition and hydration at the end stage of life cause suffering? 18th International Nursing Research Congress Focusing on Evidenced-Based Practice, Vienna
Chapter Six

A discourse analysis of difficult clinical situations in relation to nutrition and hydration during end of life care

Chapter Six is published as:

Introduction

This qualitative study examined how doctors and nurses approach, challenging situations when it comes to nutrition and hydration at the end of life. It found there were different tensions in the use of MANH in patients dying from cancer and neurological illnesses. As well it explored the concern health professionals have in regards to decision making, that takes into account quality of life versus prolongation of life.
A discourse analysis of difficult clinical situations in relation to nutrition and hydration during end of life care

Pamela van der Riet, Isabel Higgins, Phillip Good and Ludmilla Sneesby

Aim and objectives. The following discussion builds upon a previous publication that reported on the perceptions and discourses of palliative care nurses and doctors in relation to nutrition and hydration at the end of life. The aim of this paper is to report the discourses of nurses and doctors in relation to the challenges they faced when managing the care of patients with severe brain injury vs. the clearer cut situations when caring for terminally ill patients with cancer. The objectives of the study were to:

- explore the tensions in the discourses during end of life care,
- explore the challenges regarding nutrition and hydration at the end of life.

Background. The decision to withdraw life support seems to be made more readily than the decision to withdraw nutrition and hydration at the end of life. The abatement of nutrition and hydration during the terminal phase of life is a controversial issue for a range reasons. Indeed, whilst it is accepted practice in the palliative care setting, nurses and doctors often struggle with the idea.

Design. The design for this study used discourse analysis framed by a post structural framework.

Method. Focus groups were conducted with nurses working in palliative care units. Single interviews were conducted with doctors from a tertiary palliative care unit.

Results. The findings revealed contesting discourses involving quality of life and the prolongation of life.

Conclusions. The provision of food and fluid has profound emotional and social meanings for patients and families. The study reported here examined these issues with health professionals. The findings point to the challenges and tensions faced by health professionals in relation to decision making and medical hydration during end of life care. The concern is that tensions arise when decisions need to be made and how best to make these. The contesting discourses for nurses and doctors when nutrition and hydration is ceased involve maintaining quality of life vs. the prolongation of life.

Relevance to clinical practice. Medical and nursing staff have different attitudes and beliefs towards end of life care. Tensions arise when decisions need to be made based on quality of life or prolongation of life. The successful merging of curative and palliative care is not without challenges. There has been little exploration of this situation.

Key words: end of life care, hydration, nurses, nursing, nutrition, palliative care

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Nursing assessment, implementation and documentation

Introduction

This paper builds upon a previous publication (Van der Riet et al. 2008) that reported the research findings on the perceptions and discourses of palliative care nurses and doctors in relation nutrition and hydration at the end of life. The following discussion focuses on the discourses relating to the withdrawal of nutrition and hydration in difficult clinical situations involving neurological patients with severe brain injury.

One of the major goals of palliative care involves improving quality of life and providing relief of pain and distressing symptoms. All health care workers will encounter end of life situations. Indeed, health care workers are inevitably the first line caregivers when death is imminent. In particular, this is often the task of nurses.

White et al. (2001) argue that there is a gap between scientific knowledge and understanding and clinical education regarding palliative care and end of life care. The transition from a curative approach to care to a palliative and end of life care is not always smooth. Indeed, decision making for health care professionals can be fraught with tension and anxiety. The transition in thinking about a curative approach to care, to palliative and end of life care, has been referred to as ‘changing lanes’. Changing lanes can be difficult for decision makers, yet, according to Ashby et al. (2005) one of the goals of health promoting palliative care is to ‘encourage reorientation towards a natural death’.

Tensions also exist from the perspective of families and no doubt impact on the decision making of health care workers. As Ashby et al. (2005) argue:

Despite polls reporting a widespread public pragmatism about death and dying (‘I would never want to be a vegetable’, ‘When my time comes I do not want to be kept alive artificially’), when clinicians do try to discuss treatment abatement with patients and families, they often meet disbelief, even hostility.

The decision to withdraw life support, such as mechanical ventilation or withdraw medications appears to be more palatable than the idea of withdrawing nutrition and hydration at the end of life. The abatement of nutrition and hydration during the terminal phase of life is a well documented and contentious issue. Whilst it is accepted practice in the palliative care setting, it remains a clinical situation that nurses and doctors often struggle with in general care.

It has been argued that, whilst eating and drinking is an important part of our daily lives, it is not uncommon for health care professionals such as nurses and doctors to be uncomfortable and nervous about discontinuing nutrition and hydration for the patient at the end stage of life. Family members may ask for medically administered nutrition and hydration because they fear that their family member is ‘starving to death’ or ‘thirsty’. Further, health care professionals may be viewed as complicit in the patient’s death.

In palliative care practice, the provision of medically administered nutrition and hydration may occur for selected patients during the course of their illness, but it is rarely provided during the terminal phase. It is a normal part of the dying process for there to be a measured reduction and cessation of nutrition and hydration.

Van der Riet et al. (2006) conducted a qualitative study where they interviewed terminally ill patients and family members about fluid and nutrition at end of life. Their findings revealed that patients did not complain of hunger or thirst. On the contrary, with the measured but moderate reduction of oral intake there were no dramatic ill effects, such as complaints of hunger or thirst associated with starvation. However, this palliative care experience is not widely known among health professions, or the wider community. Even in the medical profession there has been disagreement regarding the provision of medically administered nutrition and hydration for terminally ill patients.

As health care workers, we need to understand why the abatement of treatment at the end of life poses difficulties for us and for families. In particular, the provision of food and fluid has profound emotional and social meanings for patients and families. The study reported here examined these issues with health professionals. The findings of this study show that, when the need to ‘change lanes’ is sudden, when death is deemed imminent, there are often challenges for patients and their families as well as doctors and nurses. The contesting discourses for nurses and doctors when nutrition and hydration is ceased involve maintaining quality of life vs. the prolongation of life.

Research question

The research question guiding the study was:

In what ways do medical and nursing staff members make sense of the provision and non-provision of medical nutrition and hydration at the end stage of life?

Aims of the study

The aims of the study were to:

• explore the tensions within the discourses during end of life care.

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explore the challenges nurses and doctors face when negotiating with families regarding nutrition and hydration at the end of life.

Methodology

Discourse analysis was used as a method to explore the discourses and challenges. Discourse analysis is a widely used qualitative technique that has been adopted in public health, sociology, psychology, education, linguistics and communication. The methodology of discourse analysis provides insight into the bodies of knowledge as they are contextualised (Cheek, in Powers 2001). Discourse analysis may be undertaken in different ways; however, the goals and assumptions are common. A discourse is a ‘group of ideas or patterned ways of thinking which can be identified in textual and verbal communications and can be located in wider social structures’. In discourse analysis, patterns of meanings called discourses are explored and analysed. Importantly, discourses regulate particular practices and in the context of this paper what care is possible and desirable at the end stage of life.

We have drawn on the writings of Foucault (1983), French philosopher and historian, to explore the principles and grids of meaning that underpin peoples’ ways of thinking and doing. For Foucault, discourses are derived from power and frequently possess ‘hidden’ power (Komesaroff 2008). Komesaroff asserts that this view is pessimistic and can exclude other possible meanings. However, we argue that the analysis of discourses provides insight into the hidden power and meanings of difficult clinical situations that would otherwise not be made visible with other methodologies. Discourse analysis in this study provided an in-depth understanding of the mechanisms and relationships of power when health care workers faced with difficult clinical situations. As Foucault (1983) has argued ‘mechanisms of power are an intrinsic part of all relations and, in a circular way, are both their effect and cause’ (Senellart 2007).

In discourse analysis one ‘seeks to understand the rules, mechanisms and structure of conversations’. Meanings from talk and text, which may not necessarily be visible, are revealed.

In the context of this study, discourse is the site for expressions of personal, moral and ethical tensions involving quality and prolongation of life when caring for people who are dying. In analysing the discourses in this study we paid particular attention to the language used by the participants, the use of metaphors and euphemisms, pronouns and binaries and subject positions. Discourses provide subject positions, which constitute subjectivities in particular ways. They authorise ways of making truth claims, such as, when making decisions to prolong life for the sake of a quality existence. Furthermore, we explored two main discourses, quality of life and prolongation of life to determine if they made sense (were they consistent and logical) and if they were conflicting. Within these two main discourses we identified other discourses such as decision making, moral and ethical codes, cure and care.

Setting of the study

The setting for the study was two palliative care units in New South Wales, Australia. One unit is a tertiary referral service and the other unit is in a major rural hospital.

Ethical considerations

The study was approved by the Human Research and Ethics committee at the University and Area Health Service where the study was conducted. All participants were provided with information letters detailing the aims and plan for the study. Whilst anonymity could not be guaranteed for the focus group participants, group members were informed of the need to maintain the confidentiality of the group discussion and the names of fellow participants. Single face to face interviews were planned with medical doctors because of the anticipated difficulties of getting them together at one time for the focus group discussion. Focus group discussions and single interviews were transcribed by a confidential transcriptionist. Transcribed discussions and interviews were de identified so as to ensure the anonymity of all participants.

Method

Following ethical approval for the study, recruitment of participants began. Nursing and medical staff, deemed potential participants for the study, were approached by the nursing unit manager (NUM) of the service The NUM briefly explained the purpose of the study and provided an information letter and consent form with a reply paid, self addressed (to the researchers) envelope.

Data were collected over six months and included two focus group interviews with nurses \( (n = 15) \) working in two separate palliative care units and face to face interviews \( (n = 4) \) with medical doctors from the tertiary palliative care unit.

Once data had been collected, the following steps adapted from Gill’s (2000) discourse analysis was used to analyse the data:
Data were read and interrogated. This involved critically examining assumptions and the sense made of realities. Data were coded as inclusively as possible. Data were analysed by examining regularity and variability.

In addition to Gill’s steps, data were analysed for contesting discourses and explored for subject positions. Foucault (1983) maintains that we take up subject positions within discourses (Senellart 2007). Particular attention was paid to the language used by the participants, focusing on the metaphors, euphemistic expressions, pronouns, overwording, meta discourse and binaries. It is important to study the use of language because ‘we are connected ...through language and through our shared corporeal presence in the world’ (Komesaroff 2008). Themes within the discourses were also identified and gave critical insight into how staff perceive, construct and communicate issues of nutrition and hydration at the end stage of life and, how this impacts their work with patients and families.

Findings

The following discussion outlines one main theme; the ‘blurring of boundaries’ and the related discourses.

Blurring boundaries

‘Blurring of boundaries’ permeates the discourses in this study and captures what it is like for the participants to be working with situations where decision making is difficult regarding end of life care, when the final outcome, in terms of a person’s death, cannot be anticipated or predicted as clearly as it is known in some clinical situations, as in cancer. In other words, decisions are not so clear cut because there is a blurring of the boundaries between what might be a decision that results in a good life before death vs. one that prolongs life and results in unnecessary suffering. Komesaroff (2008) argues that ‘death, like a language itself, is the boundary surface between the known and the unknown, between coherent, stable communities of meaning and utter chaos’.

Quality of life vs. prolongation

Evident in the data are competing discourses involving quality of life vs. prolongation of life. In the discourses regarding end of life care there is a blurring of boundaries between the discourses; quality and prolongation of life.

Actions taken to improve the quality of life may also reduce the quality of life and cause suffering. Actions taken to prolong life may impact negatively on aspects of quality and also cause suffering. To ignore the expressed desire of a person who is dying will also cause suffering. As a result, tensions arise in certain clinical situations for nurses, medical doctors, patients and family members. The following discourses reveal the possibilities for suffering. Frequently there are intersecting positions within these discourses of power, knowledge and subjectivities. Doctors and nurses have knowledge and, therefore, are in a position to exercise power; however, as Foucault (1983) reminds us, we can exercise power but we do not possess it.

An ethically difficult situation involves uncertainty and tension in what one should do so that no harm is created. This tension arises from our moral codes and the choices we have or don’t have access to. Ethics has been said to operate independently from moral codes and is about choices. This tension felt is often because the moral codes discourse contests with our subjectivities and what we believe to be regimes of truth. Discourses authorise people to voice these regimes of truth. In this paper regimes of truth often contest with not only the subjectivities of doctors and nurse but also carers and families. For Foucault meanings and truth are the effects of discourses and power (Komesaroff 2008).

In the following excerpt a doctor reports on the blurring of ethical boundaries in decision making involving stroke patients where ‘truths’ are frequently fraught with contradictions:

Yeah, ethically a lot more difficult these (neurological) patients. Cancer patients, are clearly, its part of their disease trajectory to enter the semi comatose state and then they are clearly on a trajectory towards death very soon. It’s much more difficult when a patient who has had a stroke is unable to swallow and then a decision is made usually by the family in consultation with the medical staff not to provide artificial hydration. And I must say that most families where I’ve been involved with that decision, they all, they feel comfortable that they’ve made that decision because they feel that the patient is neurologically impaired and a lifeless being, kept alive as a vegetable. And so, I mean in some ways and I think the ethical boundaries get quite blurred, because in some ways, the decision not to provide that additional nutrition is sort of a slow form of euthanasia.

The use of the metaphors, ‘lifeless being’ and ‘vegetable’ are pervasive. The metaphors depict an inanimate, inert object with no connection to the life-world. They portray a non-existent life, a life without being. This ‘impaired’ patient is neurologically impaired and a lifeless being, kept alive as a vegetable. And so, I mean in some ways and I think the ethical boundaries get quite blurred, because in some ways, the decision not to provide that additional nutrition is sort of a slow form of euthanasia.
discourse operating here involving a desire to make the
irrational rational and generate an implicit knowledge of
predictability that is, if you know that death is imminent. It is
acceptable because it is part of the dying trajectory and death
will not be prolonged and drawn out. Desire is being
operated here from a humanist discourse of predictability.
There is also a discourse of compassion to have ones actions
do no harm, do good and cause little or no suffering, as, after
all, this is what palliative care is about. However, there are
also contradictory clinical decision discourses evident. On the
one hand, the participant doctor is saying the neurological
patient, who is lifeless and who does not receive any
nutrition, experiences a slow form of euthanasia, yet for
cancer patients who are cognitively alert and dying, this is
different.

This same doctor talks more about the difficulty in decision
making and having to make choices:

So there’s a decision made that what’s required to keep the person
alive is going to be withheld, …but on any given case it’s very hard
when there is no hope of neurological improvement, why would you
continue with that?: Ah, it’s easier to make those decisions in the old
neurologically impaireed than it is in the young person who is
neurologically impaired.

There is a dualism here with the use of language ‘the old and
the young’ that privileges the young over the old and supports
an ageist view of the patient. The doctor struggles with
decision-making around young patients and does not seem to
struggle with cancer patients or older patients with neuro-
logical pathology. Later this doctor is averse to using the term
‘withholding’:

I shouldn’t be using withholding, it’s not withholding and it’s just the
non-provision of medical fluid and nutrition.

This doctor further reports:

Well in that situation I think that the malignancies are a different
kettle of fish because they have, clearly have progressive disease that
kill them anyway.

I feel you know, in some ways those decisions are much easier to
make than the ones patients who’ve had a massive stroke. I have less
trouble regarding cancer patients than I would with a forty year old
who’s had a massive intracranial bleed. I think it’s important that
nobody in the team feels that it’s their decision and that it comes
down to collaborative decision or the family’s wishes very much
respected.

For some doctors the distinction between curative and
palliative discourses involving clinical decision making are
often blurred. There is also a clinical decision making
discourse operating here that contests with discourses of
cure and palliation. This blurring of curative and palliative is
evident not only in this data for doctors and nurses but also
for patients and their families. A study by Pincombe et al.
(2003), showed that principles of palliative care are not
applied in the acute hospital setting. In the following
exemplar the doctor highlights the need to differentiate the
use of a medical intervention, percutaneous endoscopic
gastrostomy (PEG) feeding, for the purpose of sustaining a
quality of life in someone who has a future. Its use is simply
to satisfy the desire to feed someone who is terminal. This
doctor talks about the struggles in acute care and the
tensions:

I argue with many (Acute care) consultants so I quite often am asked
to come and see patients in the sort of situations you describe in
the main hospital and I feel my role is sort of facilitating the family to
come to some decisions and I don’t try to influence. I mean some
people might want to give PEG feeds, but it’s important that they
don’t see that as some...in some way going to improve their quality of
life.

Furthermore, he says he ‘tries not to influence’ but with the
level of knowledge he possesses he can exercise his clinical
power and not provide the medical intervention.

In the following, a second doctor is ambivalent about the
same medical intervention and he is not so clear how to
manage this difficult situation:

Let’s take for example a peg feeding for nutritional intake. That is the
classic for me, the use of peg feeding in (palliative) patients. There is
the debate that a patient who cannot swallow who also has other
symptoms of advanced disease, can still mobilise around and still
perform activities of daily living, but it is foreseen that that this will
change in the near future. Does the role of parental nutrition, feeds
via a peg tube or nasogastric tube, does that provide any real benefit
for the patient? Again it comes down to an individual thing. I am
fairly – I hate peg tubes. I think that they quite often provide an
option which doesn’t necessarily benefit the patient at all and
sometimes in doing these things we can be actually sending the
patient down a path to more suffering, so that would be an example
of where it becomes very difficult.

There is palpable tension here in this doctor’s voice and in his
words, ‘I hate pegs’, as the role of medical nutrition will not
necessarily benefit the patient. As he argues, it is not curative
when patients have an advanced disease. There are also lines
of fracture in the text, which open up a different path and line
of action. The doctor described this path of suffering:

If we prolonged their lives by feeding them up, keeping their nutrition
up, maintaining hydration, we maybe prolonging their lives so that in
Nursing assessment, implementation and documentation

difficult clinical situations during end of life care

the future they’re going to run into increased problems with pain, increased problems with nausea and vomiting, increased problems with this and that, a lot of the things that we see in advance cancers, so what are we saying when we put a peg tube in. We have to be wondering what are we doing this for, a quality of life perspective, or are we doing this for life prolongation. Are we likely to make this patient’s dying process more difficult than it is? For a lot of patients it is still a difficult decision. It is not automatic, that they want to live longer with a peg tube in, a lot of patients decide straight off the bat there is no way I want anything like that.

In the following, a hesitant nurse reports a contrary view held by the patient. For this patient a peg tube gives her hope that her life will be prolonged as she does not want to give in to death:

We had a peg tube in a woman here earlier this year who had very advanced motor neurone disease and you know it is questionable as to whether to do it or not, but after she got all the information she wanted to push on, but she knew all the information, she knew our hesitation.

The nurse was doubtful that the patient had made the right choice. The patient chose artificial feeding via a peg feed, with the hope of prolonging her life. The nurse does not wholly support this strong desire of the patient as she wonders aloud if this is the right decision. Evident here is that a tension also exists in what the patient desires. The patient’s desire for life to be prolonged guides her decision and this is in opposition to the nurse’s subjective desire. For some patients life under any circumstance is preferable to death.

In the following discourse involving a patient’s desire for life the nurse further emphasises this same point:

Oh, you know, you always go back to your own experiences. I just remember this one woman who...she was operated on a couple of days before she died, but because that’s the way she wanted to die. She wanted to die with tubes and everything coming out of her.

In the interviews, nurses agreed that provided the patient was dying, they did not experience any tension themselves with the issue of not providing medically assisted hydration at the end of life. However, the boundaries became blurred when a patient was unconscious and not terminally ill:

This is where I find it difficult to understand that the person’s in a coma, they haven’t actually got a terminal disease but for some reason they’re in a coma. It might be months, or even a year and they’re giving them artificial, you know, NG feeds or peg feeds. When do you know when to stop that sort of thing?

The discourses frequently referred to the tension that exists for staff between considering medical hydration as a treatment to improve the quality of a person’s life vs. the prolongation of their life. Throughout the data is a desire to seek clarity in contesting discourses of quality of life vs. prolongation of life. This is seen in the following doctor’s comments:

It is a very emotionally charged area and you also have to bear in mind the stage of a person’s disease and the possible achievable outcomes of regaining quality of life as opposed to length of life. So I think it is a very important distinction that needs to be made, because you can certainly keep people alive longer. So making the distinction between quality of life and prolongation of life is really very important and that has got to be done and that’s an important discussion that has to had with honesty with the patient and their family so that they can be informed along those lines as well as helping the family and patient, especially the family.

In considering the responses from nurses interviewed, it became clear that the boundaries between quality of life and prolongation of life are not easily managed. For example, sometimes in a situation where there is an expectation or a desire by the patient to experience a special event, subcutaneous fluids will be given. Here the boundaries between quality and prolongation of life shift because in prolonging life there is the anticipation that a special event will be experienced and, therefore, a quality of life will be experienced. Another doctor reports:

We’re much more interested when it comes to fluids in things like, do they want to survive a bit longer for a significant family event? If they do, then we’re quite happy to do what we can to help them survive for that long.

One of the nurses interviewed comments that there are some benefits in giving subcutaneous fluids, especially when a diagnosis of cancer is new as this allows patients and family member’s time to adjust to what is happening:

Sometimes with people who have recently been diagnosed (with cancer) and, they are on a fast decline, it may not help the patient, but it might help the family to begin with because it looks like you’re doing something and they want you to do something. They can’t feed them, they can’t make mum eat anything and sometimes I think it’s really appropriate to maybe give them some sub-cut fluids initially if they’re a bit dehydrated. Then, really support the family and talk to the family about what might be happening. We’ve had someone who recently went home to a very isolated area with sub-cut fluids and you know, I was a little bit distressed that that was happening because the plan was he was to have them for two weeks, but it did give the family time to accept what was happening. It was very soon after his diagnosis. I guess that’s one of the benefits. And in this case it didn’t cause any increase in discomfort that we were aware of to the patient.

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If dying takes too long

Previously, a doctor reported on a dying trajectory that was predictable. However, here we see a discourse of dying taking too long and creating distress. The following comments reveal the tension and anxiety experienced when the time of death takes a long and unpredictable course:

I do acknowledge how hard it is for families, especially if the dying process takes a long time. So if people die within one or two days, most families can tolerate that but if there’s a very long period where the patient is semi-comatose, say ten days or more, then as every day goes on the family, their level of anxiety increases. And it does get to a point where you do start feeling the anxiety yourself.

The doctor here is experiencing the transference of tension that family members experience at this difficult time. This doctor is also referring to the dying patient that is not receiving fluid or nutrition and is comatose for several weeks. For the family there are often conflicting emotions of not wanting their loved one to die, but at the same time not wanting them to ‘suffer’. The idea of human suffering is anathema to a quality life or death. That a loved one might be in pain and discomfort is too much for family members or health professionals to bear and the more powerless they feel. The longer the dying phase takes, the more tension and anxiety is felt.

Discussion and conclusion

Relevance to practice

The main theme emerging from this study was the ‘blurring of boundaries’ surrounding end of life decision making for doctors and nurses particularly in relation to the care of neurological patients where there are more uncertainties in decisions made than with the patient who is dying with cancer. Throughout the main theme, blurring of boundaries, are contesting discourses involving compassion, humanism, decision making, moral and ethical codes, cure and care. Each of the discourses involve subject positions that reflect the unconscious beliefs and attitudes of the participants we interviewed.

The findings of this study point to the tensions that exist for health care workers in relation to decision making and medical hydration during end of life care. The single biggest concern for health professionals is how best to make a decision for an individual regarding their end of life care and how best to advise family members: should decisions be based on quality life and if so, will the decision prolong life and/or cause suffering? In the situation of terminating medical hydration for patient with cancer the decision seems to be clear cut. Cancer patients have a diagnosis that is deemed terminal and often the trajectory towards death is predictable and widely known. Decision making is not so clearly evident with neurological patients because of a degree of unpredictability. As noted previously, in palliative care practice, the provision of medically administered nutrition and hydration may occur for selected patients during the course of their illness, but it is rarely provided during the terminal phase. It is a normal part of the dying process for there to be a measured reduction and cessation of nutrition and hydration. In those patients with stroke, however, tensions arise out of the inability to forecast the trajectory towards death. There is little or no hope for cure and there is little or no hope for improved quality of life but decisions are not as clear cut because the dying trajectory is rarely known.

As Larkin et al. (2007) remind us, the successful merging of curative and palliative care is not without challenges and requires sensitivity. Often boundaries are blurred between these two lines of management. The idea of a mixed management model, where curative and palliative treatments are undertaken simultaneously has been explored from a clinical viewpoint. However, there has been little exploration of this from an ethical viewpoint, as well as the impact of decision making on staff and patients. Ethical decision making needs to be explored further so that difficult situations can be better managed for dying people. Discourses of quality of life and prolongation of life give rise to different truths creating meanings and understandings. It is important to acknowledge that patients’ desire for life needs to be respected and sensitively addressed.

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Contributions

Study design: PV; IH; data collection and analysis: PV; IH; PG; MS; manuscript preparation: PV, IH, PG, MS.

References


Nursing assessment, implementation and documentation


Medical officers in acute care settings: their views on medically assisted hydration at the end of life

Chapter Seven is published as:
Introduction

This chapter is a qualitative study that examined the experience of acute hospital doctors in regard to medically assisted hydration at the end of life. It showed that these clinicians sometimes have difficulty recognising dying and there is tension between curative and palliative approaches.
Medical Officers in Acute Care Settings: Their views on medically assisted hydration at the end of life

Phillip Good, Ludmilla Sneesby, Isabel Higgins, and Pamela Van der Riet

INTRODUCTION

Most people die in a hospital in-patient setting, and they do so without specialist palliative care (1). Some hospital deaths are unexpected, but many can be predicted. In the case of expected deaths, the question of whether to withhold or withdraw medically assisted hydration (MAH) frequently arises. MAH can be given via subcutaneous or intravenous (parenteral) routes. Studies have shown that almost half the patients who die in an acute hospital setting do so with parenteral hydration continuing until the time of death (2-4). One of these studies also found that 5 percent of patients (who were terminally ill from cancer) had medically assisted nutrition at the time of death (3). Here we will focus on MAH, but nutrition at the end of life is a related aspect of care that often needs to be addressed by clinicians with patients and their families.

The use of MAH at the end of life is controversial, and practice varies across health care settings; there are strong, diametrically opposed views on what treatment should or should not be given (2, 5-7). It is a matter of concern that there is a lack of high-quality data to clearly guide health professionals as to when it is or isn’t appropriate to provide MAH at the end of life (8-10).

This study builds on previous qualitative studies conducted with nurses and doctors that explored palliative health care professionals’ attitudes toward nutrition and hydration at the end of life (11-13). We used qualitative research methodology to reveal and better understand the attitudes of specialist medical practitioners in acute hospital settings toward MAH at the end of life. Our research question for the study was:

**INTRODUCTION**

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What are the perceptions of doctors in acute care settings regarding the use of MAH in end-of-life care?

DESIGN AND METHODS

This was a qualitative descriptive study with discourse analysis as the guiding methodology. Qualitative methods provide insights into how people make sense of their experiences — insights that are not easily gained through other methods. A qualitative approach is useful in the exploratory phase of research, when little is known about the topic (14).

Discourse analysis is a widely used qualitative technique that has been adopted in the fields of public health, sociology, psychology, education, linguistics, and communications (15). It involves the study of language within social contexts (16). The social context of this study was medical officers in acute care settings and their interactions with dying patients and their carers. Study data were subjected to discourse analysis; but, as O’Connor and Payne argue (17), the term “discourse analysis” covers a range of approaches and practices related to reading and analyzing texts. The approach we used is based on the idea of discourse as formulated by French post-structuralist Michel Foucault (18). Generally speaking, “discourse,” in this context, refers to regulated ways of speaking or writing about an object or topic that enable that object or topic to be understood as truth and common sense. Discourse is concerned with the ways in which knowledge and truth are constructed and with issues of authority and power relations within institutional contexts. O’Connor and Payne argue for its efficacy in these terms: “a) Discourse analysis provides a legitimate way of balancing many perspectives of an issue without needing to establish the correctness of any one perspective. b) The method is reflective, open-ended in the questioning of text, rather than seeking solutions or developing a dominant view” (17).

For the purposes of this study, discourse is the way in which health care professionals express their thoughts, actions, and behaviours through language when addressing the quality and prolongation of life of people who are dying. In analyzing discourses, we paid particular attention to the language used by the study participants — metaphors and binaries, the dualities or tension points in the conversation. Specifically, we looked at how discourses about attending to dying patients constructed doctors’ perceptions and views on providing MAH in end-of-life care. Discourses authorize ways of making truth claims in certain situations, such as when decisions are being made to prolong life based on the patient’s quality of existence. Discourses regulate doctors’ practices — that is, they inform, prescribe, and direct how a doctor acts and behaves in practice situations. Like social and cultural norms of behaviour, they direct one’s actions. In this study, discourse analysis allowed us an in-depth understanding of the mechanisms and power relationships at work within the difficult and sensitive context of decision making in the care of dying patients.

Study methods included face-to-face, in-depth interviews with eight medical officers. Data was collected between December 2008 and December 2009. We used a schedule to guide the interview discussions. The primary researcher presented a range of questions (such as, “Can you tell me about your experiences with dying patients?”) and encouraged participants to discuss any particular issues or concerns they had. Interviews were transcribed, confidentially, by a transcriptionist and de-identified to ensure anonymity. The transcripts were read independently by all of the researchers a number of times. Significant statements were highlighted (including those with metaphors, binaries, tensions, and opposing views). Then, with the agreement of all the researchers, the interview conversations were coded and organized thematically, under the relevant headings, into discourses. Finally, the transcripts were completely re-read by the researchers to ensure that no discourses or themes had been missed or excluded.

We recruited a purposive convenience sample of medical doctors from the medical, hematology, and oncology units of a large teaching hospital located in one area health service in New South Wales, Australia. Consultants interviewed had specialist qualifications in general internal medicine, hematology, or oncology. Purposive (or theoretical) sampling involves recruiting participants who possess characteristics that will facilitate an exploration of the phenomenon being studied (19). We conducted individual face-to-face interviews with participants because we anticipated that it would be difficult to schedule these professionals for a focus group discussion.

Approval for the study was granted by the Hunter New England Human Research Ethics Committee. All participants received information letters detailing the aims of, and plan for the study.

RESULTS

The main discourse to emerge from this study was linked to the professional and personal struggle involved in attending to those who are dying.
Within this main discourse is a discourse of uncertainty that transcends the professional and personal struggle. This discourse of uncertainty is associated with the transition from a curative to a palliative approach to care, consultation with patients and their families, the cultural expectations of patients and their families, the effects of dehydration, and technology and the influence of media on expectations of cure over care. Due to its pernicious nature, the uncertainty discourse becomes a battleground for some medical officers when they realize the futility of treatment. In this section, we provide interview excerpts to demonstrate the ways in which discourse becomes a site for professional and personal struggle.

Uncertainty: The Transition from a Curative to a Palliative Approach

When a patient enters the end-of-life stage in an acute hospital setting, he or she may have already experienced a long period of declining health and multiple interventions. These interventions may have once worked, but now they are no longer of benefit. The transition from active treatment to palliative care can sometimes be clouded with uncertainty over expectations related to the patient’s deterioration.

“In those patients who all this fails and are going to die from their condition, there usually becomes a stage where they transfer from a curative approach to a palliative approach...end-of-life care. And that’s always difficult for the patient because, you know, well, they don’t want to die.”

“I mean there’s nothing nicer than being able to cure someone. And then negotiating the fact that the treatment hasn’t been effective in this patient, and it varies from person to person...it’s usually not an easy road.”

These quotes from study participants not only exemplify the difficulties doctors have in clinically recognizing when treatment is no longer effective, but also how emotional this transition can be for them, especially if they have been involved with the patient for some time and have established a relationship with the patient and the patient’s family. Metaphorically, the phrase “not an easy road” indicates that the doctor may have shared part of the patient’s rough journey. There is tension here and a competing discourse of cure versus palliative care. The patient’s transition to palliative care has not been easy for this doctor, and there is a pervasive discourse of uncertainty. The knowledge and assessment skills derived from professional practice do not seem to provide comfort to this doctor.

Consultation with Patient and Family

Coupled with the experience of this uncertainty is the need to communicate with the patient’s family. For the first time, the fact that the patient may be dying must be broached. The family needs to adjust to this possibility, and time becomes important — time is required to assist family members to come to terms with what is happening to their loved one.

“I think it depends on how much time the family have had to, well — it depends actually on the family themselves, their cultural background, how much time they’ve had to adjust to the situation. Obviously, if you’re dealing with a family who haven’t come to terms with it, either because it’s happened too fast or for other reasons, then they will often worry and ask why their relative isn’t continuing to receive intravenous fluids when you’ve stopped it...and will become disturbed if you remove them without discussing it with them or without giving them some warning.”

Talking about withdrawing MAH can seem confrontational to family members who are coming to terms with the impending death of a loved one. To cease MAH is to cease treatment that is linked to a discourse of cure, hope, and life; the discontinuation of treatment thus leads to a discourse of hopelessness and abandonment. The doctors who participated in this study engaged in protective discourses and sometimes avoided discussions about discontinuing treatment because they did not want to upset patients and their families. These protective discourses may also have helped them to protect themselves — that is, they allowed them to avoid entering a potential battlefield. As one doctor put it:

“But it is better and it is usually necessary to involve the patient and their family in making decisions about active treatment. Because negotiating with patients and with family members, in reasonable ways, is an important part of securing the comfort of a patient — I mean when they’re dying. And so you do that, and then you might discuss with the family, ‘Well, what more will we do?’ Sometimes, and I don’t think this is at all improper, families might need time either to arrive [at] or to come to terms with likely death of their relatives. I find most families, once it’s explained that there is no more that can be done, aren’t particularly keen to have intravenous fluids still running.’

Cultural Expectations

Conversations held and decisions made concerning dying patients can be influenced by the cul-
tural backgrounds of the patients and their families.

“Some people clearly come from a background where they expect everything to be done, and that if everything’s not done, then the patient’s been abandoned. And if they don’t insist that...everything possible be done then...they are failing in their duty in some way. I wouldn’t say that [is] characteristic of any sort of particular ethnic or religious group.”

The way in which doctors approach these conversations can also be influenced by their own cultural backgrounds.

“But culture comes in a little sometimes with our doctors. Some doctors come from cultures where they are very uncomfortable with withdrawing care.”

Effects of Dehydration

There were conflicting views among participants as to what effects dehydration could have on patients at the end of life, as evidenced by these extracts from two interviews:

“I mean, obviously dehydration’s uncomfortable.”

“[There is] some empirical evidence that there was not really an issue of suffering from dehydration in people who...were dying naturally.”

In material derived from the interviewer’s notes, the first doctor says, “we can’t have patients die of dehydration”; the interviewer reports that “the situation had to be negotiated with the patients, and in [the doctor’s] experience, there were no benefits to dehydration...it had...the potential to hasten [patients’] demise, but not by a material extent.” But later in the same interview, the doctor says that he is “perpetually surprised by how long [people] can live for without...food and fluid”; he also observes that such patients “did not appear to suffer.” Like the other senior doctors in the study, this participant said that younger doctors and nurses who lacked his experience and knowledge were reluctant to discontinue MAH because they believed that this was distressing for the patient. Another senior doctor expressed the view that terminal dehydration was not “an advantage or a disadvantage;” but he also cited an overseas study that had concluded “it was not an uncomfortable process.”

Study participants gave different opinions as to whether terminal dehydration was beneficial or detrimental to the patient; there was a lack of consensus and some confusion on this issue. However, participants did acknowledge that natural dehydration does not appear to cause suffering or discomfort.

Technology and the Influence of Media

Another prominent discourse that emerged from this study was technology and the influence of media. This discourse addressed the influence that television has on the perceptions and expectations of patients and their families related to what medical interventions can achieve. For example, two doctors commented on the ways in which popular culture and technology impact upon the decision-making process.

“Clients, patients, family? And they see all these emergency programs about intensive care or what can be done, so they actually have tools to deal with what’s going on...and it makes things easier.”

“We’re still basically television-driven consumerists...it seems to me that the majority of people now have their experience and understanding of the health care system from television...and movies, and their expectation of what will happen seems to be significantly affected by what they’ve seen on television.”

There is a binary involving a positive response and a negative response in this discourse. The first response recognizes an educative potential in popular culture media, and the second response registers concern about the threat such media represent to the doctor’s authority and about the impact they have on patients’ expectations. These opposing discourses reflect the notion of cure versus comfort during end-of-life care. The fact that people know “what’s going on” heightens expectations of treatment, intervention, and cure. Popular culture media have a strong influence on the perceptions of the general public. The technology and consumerism discourse authorizes its own truth claim of knowledge, placing it above that of the medical discourse.

Hydration as Symbolic

Medical intervention can be seen as a form of caring and thus as a symbolic gesture. In speaking about medical interventions for dying patients, one doctor said:

“At that stage, I would try and eliminate discomfort for the patient, and having an IV is a discomfort; you can’t wash...and, and, so in a attempt to, sort of — I mean, it’s a symbolic gesture as well that we are ceasing medical care and there’s nothing more symbolic of medical care than a drip in your arm. You can’t miss out on a drip in your arm if you come to hospital, so, having a drip in the arm is one of the symbolic gestures we make...when we go down that path.”

This doctor acknowledges that intravenous therapy may cause discomfort but that it is a pow-
erful symbol of hope. This reflects doctors’ need to be seen as doing something, as caring by intervening and not giving up. It is also an attempt to avoid a discourse of helplessness.

Uncertainty as a Battleground

The decisions that are made by different participants in end-of-life care are often metaphorically expressed in a dramatic, warlike way. For example, speaking of family conflict during this period, one participant reports that it’s “sort of a minefield and battleground.” The doctor is positioned as a major “player” in this drama. A power struggle plays itself out on the “battleground,” with patients, family members, and doctors all vying for control against a background of helplessness in the face of inevitable death. Metaphors such as the end-of-life stage as a “journey,” “there’s these games going on,” and “all of life is a play and a drama, and the patient is on some kind of stage” are powerful and have underlying meanings. The emotional turmoil of the medical officer, which unfolds on this “stage,” is experienced by that person as if he or she were an actor, on show, the centre of attention — the one who is looked to for hope, for meaning, for guidance. One participant uses the metaphor “it’s like playing ping-pong,” which suggests that the uncertainty that arises when decisions must be made about a patient’s transition from curative to curing, may therefore avoid or postpone these discourses.

The Futility of Treatment

Usually, once the deterioration in the patient’s condition becomes clear to both doctors and family members, a plan is made to cease MAH. Again, the discourse of uncertainty of prognosis is broached.

“If somebody is not likely to survive for very long at all and a decision has been made to cease active treatment and treat symptomatically, often I would tend to not give them any sort of artificial means of hydration and just let them, if, if they’re conscious and able to, to eat and drink, let them do so. So...I guess if people are imminently dying, that to me is a different situation; too often we will be presented with somebody who comes into hospital acutely sick...you’re not quite sure what the end outcome is going to be, and usually, often, we will sort of initially, at least, treat people with, with intravenous fluids, if they, if they’re not taking in enough by mouth. Initially, and then until it’s clear what the prognosis is and, and sometimes then we will discontinue the intravenous fluids if it’s going to be a, a futile treatment.”

Participants saw MAH, in this kind of situation, as prolonging the dying phase rather than making the patient more comfortable. The futility of treatment constructs doctors’ views on how MAH should be managed for dying patients.

“My feeling is that, if a patient is not likely to survive for long, then it’s not helpful to do anything....”

In the end, there may be some disagreement between the medical team and the carers as to when to withdraw MAH.

“Well, I, I don’t think we’re obliged to comply with the wishes of a family if, if it’s a treatment that we think is futile and not helpful. But, I mean, by the same token, you, you try not to, you know, upset relatives or if, if they thought that there was some benefit, I mean perhaps, perhaps, you know, you can be willing to, to keep the fluids going for a while more while you...keep talking to them on each day and, and often they will sort of come to realize that it’s not practically helpful.”

DISCUSSION

The vast majority of patients who die in palliative care units have a diagnosis of cancer, whereas many patients who die in an acute hospital setting do so from a chronic non-malignant illness. Patients often live for many years with these illnesses, enduring periods of hospitalization and episodes of acute deterioration. There is often uncertainty about illness trajectories, especially in patients with a non-malignant diagnosis. The uncertainty discourse associated with prognosis influences the approach of medical specialists in the acute hospital setting when it comes to MAH at the end of life.

Discussions with patients’ families about end-of-life interventions are essential, as they enable families to make informed decisions. However, due to the difficulty of predicting the dying process, discussions between medical officers and patients’ families about end-of-life care and the withdrawal of MAH may come too late. Discussions about the cessation of futile treatment are difficult and emotional for all concerned. Medical officers in acute care settings, whose focus is on curing, may therefore avoid or postpone these discussions.

In a study involving palliative care professionals that explored nutrition and hydration during end-of-life care, there was a perception that the perspective of acute care professionals on this issue is different from that of palliative care professionals (12). The findings of our study reflected
a belief that at some stage MAH becomes “futile” and there is a need for health care professionals to “walk” with families who have a loved one at the end-of-life stage in order to help them recognize that futility. This belief was tempered with feelings of uncertainty related to prognosis; this uncertainty, in turn, has implications for patient care and the perceptions of patients’ families. The interviews we conducted with the doctors in our study also revealed conflicting discourses on the effects of dehydration — a conflict that was not present in interviews with palliative care professionals [20]. Some of the acute care doctors in this study wondered whether dehydration was painful and added to the burden of patients at the end of life, although this was not a universal concern. There was no recognition or suggestion among our study participants of possible adverse effects of MAH on dying patients. This may indicate that these doctors were still engaged in active mode/curative discourses and saw hydration as beneficial in an acute care setting; it could also indicate that participants lacked knowledge of palliative care and care for the dying.

It can be difficult to diagnose dying, as deterioration may be gradual and the focus is generally on cure. To acknowledge that a patient is actually dying may be to acknowledge that curative measures have failed. Participants admitted that administering intravenous fluids can be seen as doing something, and that it is thus symbolic of hope and caring. For this reason, families of dying patients can tend to cling to this medical technology, however futile. However it is important to remember that when death is inevitable, the focus of care should be palliative, and burdensome medical interventions need to be reconsidered.

The doctors who participated in this study did not consider the benefits or possible drawbacks of MAH; neither did they mention the possible benefits of the natural dehydration that normally occurs during the dying process. (Research indicates that at the end of life, the body’s natural opioids — endorphins and dynorphins can be released, eliminating hunger and bringing further analgesia and anaesthesia [21]).

The administration of MAH involves complex decision making. The decision to commence parenteral hydration must be based on its potential benefits, burdens, and risks to the individual patient, as well as on the discomfort it could cause. The patient’s cultural and religious beliefs must also be considered, and attention must be given to clinical presentation and goals of care. Families and caregivers require education and support if they are to accept decreased oral intake at the end of life as a natural, non-painful part of the dying process. To help them to cope with feelings of hopelessness, loss, and fear, families should be encouraged to enhance patient comfort by frequently providing oral and skin care and by being there; health care professionals can cope with their own feelings of helplessness by providing effective symptom and pain management.

Health care professionals have a responsibility to initiate early discussions about end-of-life strategies with dying patients and their families and to support and educate these families in their decision making. Families need to be informed about end-of-life symptoms, and all health care providers need to be taught how to offer comfort measures and mouth and skin care. It is also essential for health care professionals to recognize clinical situations in which a patient’s condition is reversible. MAH should be considered when dehydration results from potentially correctable causes (for example, due to treatment with diuretics and sedatives, or due to recurrent vomiting, diarrhea, or hypercalcemia).

Among study participants there was consensus that MAH should be withdrawn or withheld when it was deemed futile, but they also acknowledged that they needed to be “doing something” — that is, to be offering such treatment as a symbolic gesture of caring. Caring can be demonstrated in many other ways, but the doctors in this study saw the withdrawal of IV fluids as the withdrawal of medical care.

Given that there seems to be a lack of understanding and knowledge about the effects of dehydration — some doctors still wondered whether it was painful — more education is required about the effects of dehydration on the dying patient. Also required is further research related to the impact of reduced intake on dying patients in their last days and hours in order to support those involved in the complex decision-making process that is part of end-of-life care.

CONCLUSION
This study has focused on the discourses in which medical officers engage as they recognize the dying process and negotiate a patient’s transition from curative to palliative care. This transition can be an extremely emotional one for the doctor, particularly if the patient is someone who has been under his or her care for some time. The stress and tension experienced by these doctors as they communicate with patients and their families about end-of-life issues, such as whether to withdraw or withhold MAH, is revealed by the study.

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REFERENCES


Chapter Eight

The effectiveness and adverse effects profile of "burst" ketamine in refractory cancer pain

Chapter Eight is published as:
Introduction

Clinical trials on medications are as important in Palliative Care as they are in all aspects of medical practice. There are two particularly difficult areas of pain control in Palliative Medicine - refractory pain and breakthrough pain. Two studies were performed to look at medications to help control refractory pain. This prospective, open label, trial was a follow up study that examined a “burst” ketamine protocol in an expanded number of patients and centres.(38) It found that ketamine seemed to be effective and safe to use in this format.
The Effectiveness and Adverse Effects Profile of "Burst" Ketamine in Refractory Cancer Pain: The VCOG PM 1-00 study

Kate Jackson, Michael Ashby, Deb Howell, Jennifer Petersen, David Brumley, Phillip Good, Maria Pisasale, Simon Wein, and Roger Woodruff

[Key words: refractory pain, cancer pain, "burst" ketamine, palliative care]

Abstract / This multi-centre study of adjuvant "burst" ketamine in palliative care in-patients documents its effectiveness, duration of pain relief, and adverse effects (AE) profile. Patients received a three-to-five day continuous subcutaneous infusion (CSCI) of ketamine escalated from 100 to 300 to 500 mg/24 hours if required. When the effective or maximum tolerated dose was attained, the infusion was continued for three days and each patient assessed as a responder or non-responder using strict criteria. The response rate was 22/44 (50 percent), with 4 (9 percent) becoming pain-free. Pain relief lasting two or more weeks was documented in 50 percent of responders. AEs were documented daily using the National Cancer Institute (NCI) Common Toxicity Criteria 0-4 scales. There were 11 grade 3 and 4 neurological AEs. However, no responders elected to cease treatment early due to neurological AEs. We concluded that this protocol in the controlled environment of an in-patient PC unit is relatively safe and simple with reasonable effectiveness.

Résumé / Ce rapport rend compte d’un essai clinique multicentre portant sur l’usage de la ketamine chez les patients hospitalisés dans un service de soins palliatifs. Il décrit l’efficacité, la durée du soulagement de la douleur, et le niveau des effets secondaires de la ketamine comme adjuvant analgésique administrée en dose élevée sous forme sous-cutanée sur une période de trois à cinq jours pour les douleurs cancéreuses refractaires. Les patients ont reçu une perfusion sous-cutanée de ketamine dont la dose allait en s’intensifiant de 100 à 300 et jusqu’à 500 mg sur une période de 24 heures si nécessaire. Lorsque la dose efficace ou la dose maximale tolérée était atteinte, la perfusion se poursuivait durer trois jours pour être ensuite discontinuée. Chaque patient a été évalué individuellement selon les critères stricts de réaction au traitement, soit que le patient réponde ou soit qu’il ne réponde pas au traitement. Les effets secondaires ont été consignés à tous les jours à l’aide de l’échelle de toxicité de l’Institut national du cancer (National Cancer Institute 0-4 Common Toxicity Scale). Au cours d’une période de 26 mois on a recruté 44 patients. Le taux de réaction au traitement a été de 22 sur 44 patients (50%) dont quatre d’entre eux étaient totalement sans douleur selon l’échelle d’évaluation verbale. On a rapporté un contrôle de la douleur de deux semaines ou plus (maximum 12 semaines) chez plus de 50% des malades. On a établi au total 11 cas d’effets neurologiques secondaires grade 3 et 4, cinq malades ayant réagi au traitement et six étant sans réaction, ce qui équivaut à 42% de l’ensemble des effets secondaires de grade 3 et 4. Cependant, aucun des patients n’a voulu cesser le traitement en raison de ces effets. Nous avons donc conclu que ces résultats (dans les limites d’une étude ouverte non-randonnée) suggèrent que le protocole utilisé dans le cadre surveillé d’un service de soins palliatifs est relativement sécuritaire, simple, efficace, et aux coûts raisonnablement modérés.

INTRODUCTION
Randomized control trial efficacy evidence is still awaited for the use of adjuvant ketamine for refractory cancer pain; however, clinical experience supports this use (1-5). Indeed, as Bell and Kalso state, “time and time again, we have seen that ketamine can help solve a difficult pain problem” (6).

Acceptable cancer pain control is usually reported as being achievable using the World Health Organization ladder approach, but up to 20 percent of patients fail to achieve acceptable and enduring control using this method (7, 8). Refractory pain is particularly common with cancer-associated neuropathic pain (that is, pain due to nerve damage caused by tumour compres-
sion/invasion), with bone-metastases-associated incident pain (7, 9), and when poor opioid clinical responsiveness and/or opioid tolerance appear to be present (2). Treatments for these patients include adjuvant analgesics, radiotherapy, chemotherapy and hormonal therapy, invasive anaesthetic or neurosurgical pain-relieving procedures, and, occasionally, orthopaedic or other surgical interventions. Many patients, for pragmatic reasons — including geographical location, limited local experience, cost, patient reluctance, and inability to access pain or specialist palliative care services — cannot be considered for these more specialized techniques. Pharmacological approaches to refractory cancer pain management, especially those that have putative anti-hyperalgesic and anti-pronociceptive properties (10) and that can reasonably be deployed in all settings, are therefore necessary.

Adjuvant subanaesthetic-dose ketamine is now widely used in pain medicine, and it has a key role in helping treat refractory pain relatively simply and cheaply. This use of ketamine as an adjuvant analgesic agent differs from ketamine's original high-dose use as a dissociative general anaesthetic agent. It has been the subject of systematic analyses for post-operative pain (11, 12), a blinded randomized controlled trial (RCT) for ischemic pain (13), and a retrospective analysis of patients with chronic regional pain syndrome (CRPS) (14).

Studies of ketamine in cancer and palliative care practice have so far been open-label, and in some cases retrospective, using variable response criteria and with small numbers. Most have been positive but were excluded from Bell, Eccleston, and Kelso's 2003 systematic analysis (3). Only two studies with a total of 30 patients met their inclusion criteria. One was for adjuvant intrathecal ketamine. The other study consisted of 10 patients, each receiving three treatments in a randomized manner — that is, ketamine 0.25 mg/kg, ketamine 0.5 mg/kg, and saline as slow IV infusions over 30 minutes. Ketamine, but not saline, was effective in reducing pain intensity, but with hallucinations occurring in four patients and an unpleasant "empty head" sensation reported by two patients. No long-term double-blind crossover study has yet been reported.

In 2001, we reported on an open-label audit of 39 patients treated with a "burst" (that is, three-to-five-day) ketamine protocol in four palliative care services, located in the state of Victoria, Australia, in which an overall response rate of 67 percent was seen (1). This current paper presents the data from a subsequent prospective single-arm study that enrolled a further 44 patients from an expanded group of centres using the same "burst" protocol. The study being reported was performed to ascertain whether the early promising results would continue to be seen as local experience with this protocol increased. Additionally, perhaps as a legacy of the high-dose/anaesthetic use of ketamine, there is some disquiet as to the potential AEs profile, even when ketamine is used in sub-anaesthetic doses. We therefore elected to document rigorously each day any AEs using the National Cancer Institute (NCI) Common Toxicity Criteria 0-4 scales for neurological, cardiovascular, gastrointestinal, and dermatological (including injection-site toxicity) adverse effects.

METHOD

Patients

Between March 2002 and May 2004, 43 evaluable patients were recruited from eight in-patient palliative care centres in Victoria, Australia, and one patient from Christchurch, New Zealand. The study protocol had received ethics committee approval at all participating sites and all patients gave written informed consent. The clinical investigators were all members of the Palliative Care Clinical Research Group (PCCRG) of the Victorian Cooperative Oncology Group (VCOG) at the Cancer Council Victoria.

To be eligible, patients had to have had refractory cancer-associated pain (defined as pain with a recorded verbal rating scale [VRS] of at least 4/10), that had failed to respond to a combination of an opioid, an anti-inflammatory (steroids and/or NSAID), plus, when indicated, at least one anti-neuropathic adjuvant analgesic.

Inclusion criteria were patients: 1) with a documented pain score of at least 4/10; 2) conscious and able to participate in the monitoring of pain and adverse effects; 3) over the age of 18; and 4) able to give written informed consent.

Exclusion criteria were in line with the standard exclusion criteria for ketamine as a general anaesthetic agent (15) — that is: 1) patients in whom significant hypertension or tachycardia would be potentially dangerous (for example, those with unstable angina, a past history of hemorrhagic stroke, or raised intracranial pressure); and 2) patients with any psychiatric or other disorder that would impair their ability to give informed consent.

The majority of patients were recruited from two centres, but not all patients treated with ketamine at these centres were enrolled in the study. The reasons for non-recruitment were unclear, but they included: treatment started out of hours, treatment started before admission to the special-
ist palliative care unit, and the fact that there were limited resources and research infrastructure, particularly in the smaller units. With hindsight, it would have been useful to provide all sites with a screening log, which we could have used to discuss the reasons for not registering patients. Patients were registered centrally at the Clinical Trials Office, Cancer Council Victoria, and assigned a unique subject code number. Case report form (CRF) binders were provided for each participant. Seventy-five percent of the source data was verified in an audit conducted by Cancer Council Victoria staff during monitoring visits.

Study Design

The design was an open-label study of effectiveness, duration of effectiveness, and incidence of AEs of a "burst" ketamine CSCI at three dose levels: 100, 300, and 500 mg/24 hours, as previously reported (1). All other medications remained constant, except that we allowed a reduction in maintenance 24-hour opioid and top-up/breakthrough opioid dose as required. Additionally, benzodiazepines and/or haloperidol could be used prophylactically or therapeutically to minimize adverse psychotomimetic adverse effects.

Data Collection

Demographic data, primary malignancy, distribution and site/s of metastatic disease, comorbidities, concurrent medication, and sites and mechanisms of pain were documented on admission. Mean individual patient VRSs for the 24 hours prior to admission, 24-hour opioid/s dose, number of breakthrough (NOB) opioid doses, and all analgesics and adjuvant analgesics were recorded. Pain was classified clinically as somatic (bone metastases, mucositis, and other), visceral, or neuropathic using methodology developed earlier (1).

During the infusion and 48 hours afterwards, dedicated assessment charts were used, and the following observations were recorded: 4 hourly VRS scores, daily 24-hour maintenance opioid analgesia and all opioid breakthrough doses with twice daily pulse, blood pressure, respiratory rate, temperature, and oxygen saturation.

Additional information, collected daily, included: Eastern Cooperative Oncology Group (ECOG) performance status (0-4 scale: 0=fully active, able to engage in all pre-disease activities without restriction; 4=completely disabled, totally confined to bed or chair) (16); NCI Common Toxicity Criteria scales (0-4 scales to grade potential neurological, cardiovascular, dermatological, and other toxicities) (17); and NCI odynophagia daily grading for mucositis patients, and CSCI site inspection.

Pain Relief Evaluation

After three days of an effective — or the maximally tolerated — dose, the infusion was ceased and the response assessed. The response criteria were similar to those of the earlier study (1) and had been derived from a combination of a number of acute and chronic pain studies. Each patient was assessed individually as a responder or nonresponder by comparing the data for 24 hours pre-treatment with that of the last 24 hours of the ketamine CSCI. Patients were designated responders if they filled the following criteria:

- either they experienced complete pain relief (that is, a VRS of 0),
- or
- alternatively they had a 50 percent or greater reduction in mean VRS, supported by a corresponding change in at least one of the surrogate markers, which are itemised below:
  - they had a 50 percent or greater reduction in 24-hour maintenance opioid dose and/or a 50 percent or greater reduction in number of breakthroughs,
  - and/or
  - they had an improvement of at least one grade on the ECOG performance status or, for mucositis patients, an improvement of at least one grade on the NCI dysphagia/odynophagia scale.

Post-treatment Follow-up

Responding patients were not discharged until at least 48 hours after ceasing ketamine. We had aimed to collect follow-up information on discharged patients by means of a pro forma letter requesting that they fax similar data to that collected during the study to the investigator on a weekly basis. However, follow-up data was often difficult to obtain, and a retrospective search of the patient’s records and/or phone calls to the patient’s medical and/or nursing carers often was the best we could obtain.1

<table>
<thead>
<tr>
<th>Table 1 / Participant Flow through Central Trial Registration and Treatment</th>
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<tr>
<td>Assessed for eligibility</td>
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<tr>
<td>Not eligible – maximum VRS less than 4</td>
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<tr>
<td>Discontinued treatment due to death*</td>
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<tr>
<td>Withdrew due to AEs – nausea/vomiting</td>
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<tr>
<td>Not evaluable due to insufficient data</td>
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<td>Assessed for response</td>
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</tbody>
</table>

* 3 patients died during the study period, 2 from rapid disease progression and 1 from probable sepsis.

1 Full details of the protocol and copies of the CRFs are available from: ClinicalTrials@cancervic.org.au

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RESULTS
Patient Characteristics
Fifty-three patients typical of those on in-patient palliative care units were registered, of which 44 were evaluable (see Table 1 for participant flow through the trial). The demographic data was very similar for responders and non-responders. There were 21 men and 23 women. The age range was 35 to 82 years (mean 60, median 61). Twenty-three patients (52 percent) were over 60; 10 (23 percent) were over 70. The major primary malignancies were lung (nine), breast (eight), colorectal (four), head and neck (four), mesothelioma (four), and multiple myeloma (three). The detailed clinical data for all 44 evaluable patients is found in Table 2 for responders and Table 3 for non-responders.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Primary cancer diagnosis</th>
<th>Age at entry</th>
<th>Pain mechanism</th>
<th>Mean Pre-RVS</th>
<th>Mean Post-RVS</th>
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<th>Post-RVS NGB</th>
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<th>Pain at home</th>
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VRS: Patient Verbal Rating Scale; NGB: number of opioid breakthroughs; ECOG: Eastern Cooperative Oncology Group performance status; PDME: Parenteral Morphine Dose Equivalent; ND: not done/no data
*reduced from 300 mg due to adverse effects **patient extremely reluctant to take any opioids
Table 3 / Detailed Data for the Non-responders (n=22)

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Primary Cancer Site</th>
<th>Pain Location</th>
<th>Pain Description</th>
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<th>Mean Post-Rx VRS</th>
<th>Pre-Rx PMDE</th>
<th>Post-Rx PMDE</th>
<th>Pain Relief Post-Rx</th>
<th>Pain Relief Pre-Rx</th>
<th>Post-Rx PMDE Median</th>
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</table>

VRS: Patient Verbal Rating Scale; NOB: number of opioid breakthroughs; ECOG: Eastern Cooperative Oncology Group performance status; PMDE: Parenteral Morphine Dose Equivalent; ND: not done/ho data

ECOG status on admission was documented for all patients (see Tables 2 and 3); 15 (34 percent) had an ECOG of 3 or greater, and 4 (9 percent) had an ECOG of 4.

Pre-ketamine Opioids
Patients were taking a range of opioids, including morphine sulphate, fentanyl citrate, oxycodone hydrochloride, and hydromorphone hydrochloride. All opioids were converted to parenteral morphine dose equivalents (PMDE) using standard conversion tables where necessary (18). Pre-treatment PMDEs ranged from 3 mg/24 hours to 1,050 mg/24 hours (mean 214 mg, median 160 mg). Details of the pre- and post-opioid data are included in Tables 2 and 3.

Pain Relief
Tables 2 and 3 include the detailed pain data on all patients. A total of 22 of 44 evaluable patients (50 percent) were classified as responders, with four (9 percent) achieving a VRS of 0. Twenty-eight (64
percent) of evaluable patients had neuropathic pain, and 14 (32 percent) had somatic pain — 11 (25 percent) due to bony metastases and 3 (7 percent) due to chemo/radiotherapy-induced mucositis. All three mucositis patients were responders and there were an approximately equal number of responders and non-responders in the other two groups.

**Ketamine Doses**

A total of 17 of 22 responders (77 percent) required 300 mg of ketamine or more, with 9 (41 percent) requiring 500 mg/24 hours. These doses are generally higher than those used post-operatively and exceed the 2.5 mg/kg/min dose (equivalent to 290 mg/24 hours for an 80-kg patient) cited by Schmid, Sandler, and Katz (11) as the dose below which adverse psychotomimetic effects should be rare.

**Survival Time**

Only 24 patients were still alive at the end of four weeks, with nine surviving six months or longer. Of the two longest-term survivors, both responders, one had a slow-growing parotid tumour and the other had no apparent active disease after radical surgery and radiotherapy for a head and neck tumour.

**Adverse Effects**

AEs were reported for all evaluable patients according to NCI Common Toxicity Criteria v2 on a scale of grade 0 to grade 4, and those seen are reported in Table 4. A total of 26 AEs were recorded in 22 responders, and 26 AEs were recorded in 22 non-responders. Unless there was an increase in grade, AEs were recorded only once for each patient. A total of 27 (61 percent) grade 1 and grade 2 AEs were recorded, and these were relatively evenly distributed among responders and non-responders, although responders reported more drowsiness and non-responders reported more injection site toxicity and nausea. All grade 3 and grade 4 toxicities occurred in patients who had needed 300 mg/24 hours of ketamine or more. The most frequent grade 3 toxicity was injection site toxicity, and the most frequent grade 4 toxicity was hallucinations. (It should be noted that under the NCI Common Toxicity Criteria, hallucinations are either present or absent, and when present, hallucinations are automatically classified as grade 4 toxicity, and there is no attempt to subdivide according to whether or not the patient was worried or alarmed by them). No responding patient withdrew early due to neurological Adverse effects. No clinically significant hypertension or tachycar-

**Table 4 / NCI Common Toxicity Adverse Effects Incidence (n=44)**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Responders, n=22</th>
<th>Non-responders, n=22</th>
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<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
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<tr>
<td>Confusion</td>
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<tr>
<td>Constipation</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
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</tr>
<tr>
<td>Diplopia</td>
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<td>1</td>
</tr>
<tr>
<td>Dreams, vivid/bad</td>
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</tr>
<tr>
<td>Dysphagia</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Hallucinations</td>
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<td>1</td>
<td>1</td>
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<td>Injection site toxicity</td>
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<tr>
<td>Mood alteration – anxiety</td>
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<tr>
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<tr>
<td>Vomiting</td>
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</tr>
<tr>
<td>Total</td>
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<td>5</td>
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</table>

* Under the NCI criteria, any hallucination is automatically coded as grade 4.
Duration of Response
Responder follow-up was intended to be for four weeks; however, data was only available for 13 patients. Of these, 11 had a documented response of at least two weeks — that is, pain scores still 50 percent or less than pre-ketamine and/or described as good pain control. The longest documented response was three months, after which the patient was lost to palliative care follow-up, but Head and Neck clinic notes indicate that this patient was still pain-free at three years. Three responders were re-treated with ketamine at four to eight weekly intervals — once, one three times, and the other four times — and all responded to each re-treatment.

DISCUSSION
The overall response rate was 22/44 (50 percent), slightly lower than that of the previous study (1), but four participants (9 percent) had a complete response, becoming pain-free. This is a good strike rate for refractory cancer-associated pain — that is, pain that has failed to respond to a combination anti-inflammatory (steroids and/or NSAID) and opioid dose escalation plus, when indicated, at least one anti-neuropathic adjuvant agent. This was achieved with what was, to the patients, an acceptable AE profile and with a protocol that is applicable for use in most palliative care units — at least in Australia.

Analysis by the major clinical pain mechanism confirmed that ketamine’s action is not restricted to neuropathic pain. The fact that the majority of recruited patients had pain associated with bony metastases and/or nerve compression/infiltration probably reflects the common occurrence of these mechanisms in refractory cancer pain (7, 9) plus a potential bias in patient selection arising from the results of our earlier study (1) and other studies (3, 5). Even when using the clinically determined pain mechanism as a likely predictor of effectiveness, it is not possible to predict confidently which individual patient will or will not benefit from “burst” ketamine. Nor is it possible to be sure of failure at the lower doses; thus we advocate dose escalation to the effective or maximal tolerated dose for three days before designating success or failure. Pain relief lasting two or more weeks was documented in 50 percent of responders, suggesting that a wind-down of hyperalgesic states and/or central sensitization may be occurring. There was evidence to suggest a dose-related response, with 77 percent of responders requiring at least 300 mg/24 hours of ketamine. This demonstrates that ketamine dose escalation may be required, and failure to respond to lower doses, in the absence of AEs, is an indication for dose escalation rather than cessation as ineffective.

As reported in most other studies, the major AEs were neurological, but due to the common concurrent use of benzodiazepines or haloperidol by many of the clinicians prophylactically to minimize the bad dreams, hallucinations, and spacy feelings previously reported, it is not possible to definitively link the neurological AEs seen to the use of ketamine, benzodiazepines, or haloperidol, or a combination of drugs. Whilst the reported incidence of depressed level of consciousness, hallucinations, confusion, and bad dreams cannot be downplayed (even though most were minor — that is, grade 1 or grade 2), they would likely constitute a significant obstacle to long-term and/or outpatient treatment. In this study, none of the responding patients withdrew due to adverse neurological effects. This suggests that short-term AEs maybe traded off for better pain control. Correll et al. (14), in their study of patients with CRPS, found a similar apparent willingness to trade short-term AEs for long-term gain. In contrast, in their long-term study using oral ketamine to 100 mg/24 hours for outpatients with non-malignant pain, Haines and Gaines (19) had a high dropout rate due to adverse effects.

Finally, this study confirmed the cardiovascular stability shown in the earlier audit — that is, it specifically failed to show the frequently significant and potentially dangerous levels of hypertension and tachycardia that often complicated ketamine anaesthetia in the 1970s and 1980s. (In Australia, ketamine anaesthesia has, due to its AE profile, been largely superseded by newer agents and techniques.)

The authors concur with Bell, Eccleston, and Kelso (3) that it would be desirable to have blinded RCT evidence, which the present study does not offer. However, the conduct of large, placebo-controlled, double-blind randomized trials in palliative care has been limited to date, and both we (20) and Aoun and Kristjanson (21).

2 A complete copy of the AEs CRF is available from: ClinicalTrials@cancervic.org.au
have argued for a role for prospective unblinded studies of the sort reported here. The participants who participated in this study are typical of a palliative care patient population: they are heterogeneous in terms of age, diagnosis, prognosis, functional status, confounding comorbidities, and concurrent medications. Many of them would normally be excluded from any trial by virtue of their age, performance status, or prognosis. For example: 52 percent were 60 or older; 23 percent were over 70; in 34 percent, ECOG status was 3 or greater, and in 9 percent it was 4; and only 22 of the 44 patients were still alive at four weeks. We also question the problematic blinding of patients and observers to ketamine or controls, given that both this and our previous study (1) demonstrated a significant drowsiness and/or psychotomimetic AE profile, albeit in most cases grade 1 or grade 2.

We emphasize that there are a number of limitations inherent in this open-label, non-controlled, non-randomized study that may affect the wider applicability of its conclusions. These limitations include the potential for observer bias or placebo responses and the limited follow-up achieved. However, we suggest that, pending results from RCTs, the lack of level 1/II evidence should not preclude the use of this modality in controlled in-patient conditions for otherwise refractory cancer pain.

ACKNOWLEDGEMENTS

This article was written for, and on behalf of, the Palliative Care Clinical Research Group of the Victorian Cooperative Oncology Group at Cancer Council Victoria, Australia. We thank the participating unit staff at: Austin Hospital, Gairdner Ballarat, Bethlehem Hospital, Christchurch Hospital, Geelong Hospital, Werribee Mercy Hospital, McCulloch House Monash Medical Centre, and Peter MacCallum Cancer Centre. We also thank the following individuals: Melanie Benson, Alex Burke, Shirley Bush, Zemin Cao, Ian Davis, Jane Fischer, Kate Grundy, Kate Hamilton, Susan Haynes, Tom John, Dimitrios Lypourlis, Peter Poon, Shane White, Bryan Yap, and Alan Zimet. Funding was supported by Cancer Council Victoria. Potential conflict of interest: none.

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REFERENCES

Chapter Nine

Prospective audit of short-term concurrent ketamine, opioid and anti-inflammatory ('triple-agent') therapy for episodes of acute on chronic pain

Chapter Nine is published as:
Introduction

A different prospective study was performed looking at the use of ‘multimodal’ therapy in the setting of refractory pain. This is therapy using a combination of medications aimed at attacking multiple different receptors responsible for pain transmission. This prospective audit of a new and novel approach to therapy for complex pain was also one of the few papers that have reported on pain duration and ability to relieve pain. It showed that the longer a patient has uncontrolled complex pain, then the harder it is to achieve complete pain relief. It also found that this multi modal approach was safe and effective in the small number studied.
Original Article
Prospective audit of short-term concurrent ketamine, opioid and anti-inflammatory (‘triple-agent’) therapy for episodes of acute on chronic pain
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Departments of 1Medicine and 2Anaesthesia, Southern Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University and Medicine Program, Southern Health, McCulloch House, Monash Medical Centre, Melbourne, Victoria, Australia

Abstract
Aim: This prospective audit was undertaken in order to document the analgesic response and adverse effects of concurrent short-term (‘burst’) triple-agent analgesic (ketamine, an opioid and an anti-inflammatory agent – either steroidal or non-steroidal) administration, for episodes of acute on chronic pain. The clinical hypothesis in this study is that better pain control may be obtained by simultaneous multiple target receptor blockade.
Method: The response of 18 patients is reported. The pain and analgesic requirement data for the 24 h before starting triple-agent therapy were compared with the last 24 h on the triple-agent therapy. Patients were then classified as responders or non-responders.
Results: According to stringent clinical criteria, 12 out of the 18 patients were classified as responders. The response rate was highest for somatic pain (7/9) and appeared to decrease with duration of prior uncontrolled pain. Only four out of the 18 patients reported adverse effects and all of these were minor.
Conclusions: The results suggest that this ‘burst’ triple-agent approach is safe and effective in an inpatient palliative care population during episodes of poorly controlled acute on chronic pain, and warrants further investigation to ascertain whether it gives superior results compared to the ‘gold-standard’ WHO ladder approach. (Intern Med J 2005; 35: 39–44)

Keywords: World Health Organization analgesics ladder, cancer pain, ketamine, pain relief.

INTRODUCTION
The World Health Organization (WHO) analgesic ladder has been the internationally recommended approach to the pharmacological management of cancer pain for the last 20 years. In essence, this approach is a three-step sequential progression from non-opioid to weak/low-dose opioid to strong/high-dose opioid. The addition of a non-steroidal anti-inflammatory drug (NSAID) and/or adjuvant analgesic as required is allowed at all three steps, but in order to ensure universal applicability these are not specified. Stepwise ladder escalation over days to weeks is recommended. The apex of this approach consists of an appropriate strong opioid, usually morphine, escalated as required till pain is relieved.1

The WHO ladder cancer pain management approach was deliberately kept simple, and was aimed at widespread practice change. It had its conceptual origins in the 1970s and 1980s.2,3 However, optimal implementation of this approach still leaves up to 20% of patients with poorly controlled pain.6–9 Clinically, the situations that are most frequently refractory are those where there is intrinsic damage to the nervous system (usually by tumour compression or invasion), a pronounced incident component (usually movement-related exacerbations as a result of bone metastases), skin or mucosal inflammation or ulceration, or tissue ischaemia.

The WHO ladder takes no account of pain mechanism(s) (somatic, visceral or neuropathic),10 or of the emerging experimental and clinical evidence of central nervous system plasticity, in particular the phenomenon of central sensitization. The clinical manifestations of central sensitization include ongoing and escalating pain, hyperalgesia, allodynia and relative opioid insensitivity. Ongoing nociceptive input, with or without intrinsic nerve damage, appears to trigger central sensitization. Furthermore, there is good evidence from laboratory animal data to suggest that morphine alone may exacerbate rather than relieve pain by its unopposed action at the dorsal horn of the spinal cord.11 Mercadante et al. have reported two cases of what they believe to be opioid-induced hyperalgesia with rapid dose escalation, which persisted after switching to methadone. Methadone has...
no known active metabolites, thus making opioid metabolites an unlikely cause of the hyperalgesia.\textsuperscript{12}

There is an emerging understanding of the molecular mechanisms that generate and maintain cancer pain.\textsuperscript{13} Activation of dorsal horn N-methyl-D-Aspartate (NMDA) receptors is the best understood, and therapeutically amenable, mechanism that gives rise to central sensitization. The most potent and currently commercially available NMDA antagonist in Australia is ketamine as a racemic mixture. There is increasing evidence for use of ketamine as an analgesic in subanaesthetic doses in perioperative care,\textsuperscript{14} and in palliative care and pain medicine practice.\textsuperscript{15–17} A recent randomized trial in the management of vascular pain has shown significant activity in that often refractory pain state.\textsuperscript{18} Intranasal ketamine has been evaluated alone and in combination with fentanyl for analgesia in children with forearm fractures in the paediatric emergency department at Monash Medical Centre, with superior analgesia being achieved with the combination.\textsuperscript{19} Nadeson \textit{et al.} have shown clear laboratory evidence of an opioid dose ‘sparing’ effect when ketamine is administered with fentanyl, using the rat tail flick latency test as an end-point.\textsuperscript{20} These data all point to the possibility that short-term ketamine administration may restore, or improve opioid responsiveness. We have previously reported on one patient with a slow-growing parotid tumour causing neuropathic pain, who has shown repeated responses to ketamine, over almost 3 years. Pain control deteriorates every 6–8 weeks on opioid monotherapy, other adjuvant drugs had proved ineffective and opioid dose escalation was not tolerated.\textsuperscript{21}

The use of anti-inflammatory agents, both steroidal and non-steroidal, is well established in cancer and musculoskeletal pain management, although there are differing views about their efficacy in an adjuvant role with opioids.\textsuperscript{22–24} In palliative care, they are particularly indicated for the pain of bone metastases, liver capsule distension and nerve compression. Dose escalation, with steroidal or non-steroidal agents, is generally limited by adverse effects. In this study, short-term high-dose anti-inflammatory treatment was undertaken in combination with the other drug classes.

The clinical question that forms the basis of this audit is as follows: can better pain control be achieved in a selected group of patients with severe refractory pain or high-risk syndromes (e.g. incident and/or neuropathic pain) by concurrent triple-agent therapy? The rationale for this approach was:

1. The possibility of additive or supra-additive analgesia by potent simultaneous blockade of at least three major receptor sites.
2. Prevention or reversal of opioid resistance/tolerance. Wind-up and central sensitization are major factors in opioid resistance and the combined use of an opioid, anti-inflammatory and NMDA antagonist may inhibit or even reverse this.\textsuperscript{25}

An earlier prospective audit of continuous s.c. ketamine infusion for refractory cancer-associated pain at this centre has shown an overall 67% response rate. Efficacy was maximal for chemotherapy/radiotherapy-induced mucositis, followed by incident bone pain, then tumour-associated neuropathic pain. No patient with pure visceral pain responded.\textsuperscript{26–28} A larger multicentre audit is currently underway under the auspices of the Victorian Cooperative Oncology Group (Cancer Council of Victoria) (the protocol, VCOG PM 1–00, may be viewed at http://www.southernhealth.org.au/mcculloch).

Since these results were reported, there has been a change of practice in this service. Patients with refractory or unstable acute on chronic pain, and high-risk factors for difficult pain control, are initially treated with triple-agent regimens, rather than the progressive serial addition of agents as normally advocated by the WHO approach. The inclusion of a potent injected NSAID, steroid, or both, was based on our own experience, which concurs with observations such as those by Joishy and Walsh that i.v. ketorolac produced marked opioid-sparing effects in acutely ill patients with severe cancer pain.\textsuperscript{29}

The rationale of this regimen is similar to that of ‘burst’ ketamine alone where the object was to improve pain control by reduction in wind-up/central sensitization, with the hope that the effect might be enduring after the short-term ‘burst’ exposure.

The aim of this audit was to review efficacy and safety of this triple-agent approach prior to further, more rigorous evaluation in larger studies.

\textbf{METHODS}

This was a prospective audit, over 6 months (August 2002 to February 2003), of the analgesic response and safety of triple-agent analgesic therapy. Patients were all inpatients of the palliative care service, selected for the following reasons:

1. Unstable pain control, with moderate to severe pain requiring hospital admission.
2. Poor response to prior therapy.
3. High risk (for poor control) pain mechanisms and syndromes, especially incident and/or neuropathic pain.

All patients were treated with a combination of ketamine, an opioid and an anti-inflammatory agent (either dexamethasone, or one of ketorolac, naproxen or parecoxib). Three patients were treated with both an NSAID and a steroid simultaneously. The two commonest combinations were KOK (ketamine, opioid and ketorolac), and KOD (ketamine, opioid and dexamethasone).

Ketamine, opioids and dexamethasone were infused in the same syringe-driver solutions without visual incompatibility problems. In view of the lack of compatibility information for ketorolac, and its alkaline pH,\textsuperscript{30} this drug was either infused in a separate syringe driver, or administered as an intermittent s.c. injection at 8 hourly intervals. In two patients the anti-inflammatory agent was administered orally.

Ketamine dosage was adjusted, according to response, during the observation period, within the previously published dose range of 100–500 mg/24 h, although one
patient received a peak dose of 700 mg, with eventual response, and no unacceptable adverse effects. Opioid dose was increased according to breakthrough requirements and clinical judgement. NSAID and steroid doses were not altered during the triple-agent therapy. After ketamine was discontinued, all patients continued on opioids and an oral anti-inflammatory agent.

Pain was classified mechanistically as somatic, visceral or neuropathic based on clinical, pathological and/or radiological data. Duration of the pain prior to presentation, and presence or absence of an incident component, were also specifically noted. Pain scores were recorded routinely at 4-hourly intervals on a dedicated pain chart, together with ketamine dose, adverse effects (nausea, vomiting, confusion, drowsiness or respiratory depression) and opioid breakthrough doses.

Evaluation
The data for 24 h before starting triple-agent therapy were compared with data recorded during the final 24 h of the triple-agent infusion. Patients were then classified as responders or non-responders according to the following criteria. To be a responder the patient had to: 1. Achieve a verbal rating scale (VRS) score of 0, using a graded scale where 10 = worst imaginable pain and 0 = no pain; or 2. Have had a 50%, or greater, reduction in their mean VRS. In addition, one of the following two surrogate criteria had to be fulfilled:

- 50% or greater reduction in the 24 h opioid dose or a 50% or greater reduction in the number of opioid breakthrough doses
- Improvement in mobility or function.

RESULTS
Patients
Eighteen patients were entered into this pilot study. There were 12 males and 6 females. The median age was 66 years, range 43–86 years. The malignancies were lung (7), head/neck (2), breast (2), skin (1), prostate (1), renal (2), colorectal (1), unknown primary (1), and one patient had a non-malignant diagnosis of osteoporotic vertebral fractures.

Prior opioid and doses
The majority of patients (13) received morphine, with the rest receiving hydromorphone (4) or oxycodone (1), and one patient was also receiving tramadol. All doses were converted to a parenteral morphine dose equivalent (PMDE) using a standard acute opioid dose conversion table. The median dose of parenteral morphine equivalent was 66 mg/24 h with a range of 12.5–450 mg/24 h (Table 1).

Ketamine
The highest dose of ketamine administered to each patient was recorded. The median dose was 200 mg/24 h, with a range of 100–700 mg. The median number of days of ketamine use was 5 with a range of 3–17 days (Table 1).

Response
Of the 18 patients, 12 were classified as responders (Table 1).

Adverse effects
Despite multiple medication usage, there were minimal side-effects. Two patients reported drowsiness, one patient reported confusion. A further patient reported hallucinations and confusion (with no analgesic response) at a ketamine dose of 500 mg/24 h, and ketamine was ceased. These adverse effects were not treatment limiting in any case. Routine sedative or antipsychotic agents were not used.

Potential confounding factors
Only one patient who was deemed to be a responder was identified as having had a potential confounding event. This patient had had a debulking procedure, and received ketamine during the perioperative period and had ketorolac added to the postoperative analgesic regimen.

The post-treatment PMDE was higher in 8/12 of the responding patients. The increase was usually in the range of 30–50% of the initial dose. However, in 4/8, the increase was of the order of 10% or less, and the responses seen would not normally be expected with this degree of dose increase alone. In 3/8, the increase was greater than 50%, and this may have contributed to improved analgesia. Opioid dose escalation alone had been not found to improve pain control for any of the patients prior to triple-agent treatment.

DISCUSSION
Although the numbers in this audit were small, it appears that the chance of response was:

1. Highest for somatic pain (7/9 responses), and combined somatic/neuropathic (3/5 responding);
2. Decreased with increasing pain duration.

Intrinsic to the WHO ladder is the notion of an incremental additive approach, with gradual strong opioid dose escalation. However, if response is poor to non-opioids or weak opioids, valuable time can be lost, especially if response to so-called strong opioids is also poor. Clinical experience in this (and other) services has been that the longer pain is uncontrolled, the harder it is to eventually obtain acceptable pain relief. There are compelling arguments that cancer pain needs to be controlled early on to prevent the later development of ‘refractory’ pain.

This approach is analogous to the development of modern cancer chemotherapy. Although common in the early days of cancer treatment, single agent treatment is now unusual. Tumour growth remission is induced initially by intensive treatment with several chemotherapeutic agents, often also combined with radiotherapy and surgery. Patients are supported through significant levels of morbidity (and indeed mortality) in order to achieve the best tumour control rates. ‘Spatial’ cooperation means that dose-related toxicity is spread across a range of normal tissues and cell lines, and tumour cells
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<th>Post-PMDE</th>
<th>Mean VRS</th>
<th>B/T</th>
<th>Mobility function</th>
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*Patient also received tramadol. S, somatic; V, visceral; N, neuropathic; I, incident component; B/T, number of breakthrough drug administrations per 24 h; Dex, dexamethasone; PMDE, parenteral morphine dose equivalent in mg/24 h; Pred, prednisolone; VRS, verbal rating scale.*
are killed by actions at multiple targets. If maintenance therapy is required after induction of remission, a less toxic regimen is chosen, compatible with a reasonable quality of life. The same possibility exists for pain management. Short-term intensive treatment is deployed to block nociceptive input and reduce or prevent central sensitization. Adverse effects may be supported over a few days of intensive ‘burst’ treatment, and once the nervous system sensitization has been dampened down, a low-toxicity, low-cost ambulatory analgesic regimen is put into place, usually consisting of an anti-inflammatory drug in combination with an oral or transdermal opioid. Relapse may then again be treated with another burst, and so on. Despite the relative lack of evidence from randomized controlled clinical trials, growing laboratory and clinical data indicate that the NMDA receptor blockage mechanism of analgesic action, and ketamine as the most potent antagonist at this site, cannot be ignored.

CONCLUSION

The contention is that this initially intensive, short-term triple-agent combination treatment of pain deserves further study, particularly for those who display evidence of poor opioid responsiveness, or are thought to be at high risk of this. The inclusion of other novel drug classes, for example neurosteroids, in this combined approach, will also warrant investigation.

REFERENCES

26 Ashby M, Jackson K, Martin P, White M. The incidence of adverse effects with the use of ‘burst’ ketamine: a prospective audit. 9th World Congress on Pain; 22–27 August 1999; Vienna, Austria.
Chapter Ten

Intranasal sufentanil for cancer-associated breakthrough pain

Chapter Ten is published as:

Introduction

A major pain challenge is breakthrough pain and the use of medications that are better at mimicking the characteristics of this type of pain. (39) A study looking at the safety of the use of intranasal sufentanil had been performed and the medication found to have relatively few adverse effects. (40) This follow up study looked at the efficacy and acceptability to a larger number of patients. It confirmed the feasibility of the use of intranasal preparations for treating breakthrough pain.
Intranasal sufentanil for cancer-associated breakthrough pain
P Good, K Jackson, D Brumley and M Ashby
Palliat Med 2009; 23; 54
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http://pmj.sagepub.com/cgi/content/abstract/23/1/54
Intranasal sufentanil for cancer-associated breakthrough pain

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The objective of this study was to demonstrate the efficacy, safety and patient acceptability of the use of intranasal sufentanil for cancer-associated breakthrough pain. This was a prospective, open label, observational study of patients in three inpatient palliative care units in Australia. Patients on opioids with cancer-associated breakthrough pain and clinical evidence of opioid responsiveness to their breakthrough pain were given intranasal (IN) Sufentanil via a GO Medical™ patient controlled IN analgesia device. The main outcome measures were pain scores, need to revert to previous breakthrough opioid after 30 min, number of patients who chose to continue using IN sufentanil, and adverse effects. There were 64 episodes of use of IN sufentanil for breakthrough pain in 30 patients. There was a significant reduction in pain scores at 15 (P < 0.0001) and 30 min (P < 0.0001). In only 4/64 (6%) episodes of breakthrough pain did the participants choose to revert to their prestudy breakthrough medication. Twenty-three patients (77%) rated IN sufentanil as better than their prestudy breakthrough medication. The incidence of adverse effects was low and most were mild. Our study showed that IN sufentanil can provide relatively rapid onset, intense but relatively short lasting analgesia and in the palliative care setting it is an effective, practical, and safe option for breakthrough pain. Palliative Medicine (2009); 23: 54–58

Key words: breakthrough pain; cancer; opioid; sufentanil

Introduction

Most patients with cancer-associated pain can achieve acceptable baseline pain control with treatment based on pain mechanisms and the World Health Organisation (WHO) analgesic ladder approach. However, up to 60% of patients suffer from episodes of breakthrough pain, in which there are transitory flare-ups against a background of otherwise well controlled pain.1 Portenoy and Hagens’ three month audit of inpatients in a cancer centre showed that of 70 patients with moderate pain or less and on a stable dose of opioids, 63 (90%) had at least one episode of breakthrough pain per day and that 41% of these episodes were of rapid onset, that is, within 3 min and of relatively short duration, median 30 min. In patients with multiple bone metastases, these episodes often occur with movement such as showering or walking. The standard palliative care management of breakthrough pain is to give an immediate release opioid medication, either as an oral or subcutaneous bolus as needed.2 This is known as “breakthrough” or “rescue” dosing. Given the features of breakthrough pain, the ideal characteristics of a breakthrough medication are rapid onset, early peak effect, and duration of action of no more than 1–2 hrs.1 When opioids such as morphine or oxycodone are used as breakthrough medication, either orally or subcutaneously, the effect is neither quick nor short acting. Onset is delayed for at least 30 min and the effect lasts for 2–3 hrs. Intermittent intravenous (IV) bolus dosing or patient controlled IV analgesia (as is used short-term post-operatively) is rarely feasible in an inpatient palliative care unit, and even less so in a home environment, due to the need for continuous IV access, relatively expensive and bulky devices and the risks associated in patients with poor cognition.

Compared to morphine, oxycodone and hydromorphone, the fentanyl series of drugs have higher lipid solubility (hence rapid and effective transmucosal absorption plus enhanced blood brain penetration), higher potency (hence potentially fewer adverse effects), a better therapeutic index (hence greater safety at high doses) and a shorter duration of action.3 These characteristics make
Intranasal sufentanil for breakthrough pain

Methodology

The study was conducted in two phases. An initial dose titration phase similar to the pilot trial was followed by an ongoing treatment phase once an effective and safe dose was determined for each patient. All patients were inpatients at one of three palliative care units in Australia.

Inclusion criteria were patients who had cancer-associated pain, were non-opioid naïve (on opioids for at least one week) and who had clinical evidence of opioid responsiveness. The patients also had to have had controlled background pain and stable doses of long acting opioids. Exclusion criteria were terminal phase of illness, cognitive impairment severe enough to hinder reliable verbal rating scale (VRS) reporting, an inadequate command of English to allow reliable VRS reporting, respiratory failure, a known history of substance abuse or nasal deformity/bleeding/infection such as to contra-indicate nasal drug administration.

The sufentanil was delivered by a GO Medical™ patient controlled IN analgesia (PCINA) device. This is a 5 or 10 ml bottle that delivers 0.18 ml as a fine spray with each depression of the nasal applicator. Using a 50 mcg/ml concentration of sufentanil means that there is 9 mcg of the drug delivered per spray/depression. The study was approved by the human research ethics committee at each participating institution.

Dose titration phase

Patients were shown how to use the PCINA, and then when they experienced an episode of breakthrough pain, under nursing or medical staff supervision, they used one spray of IN sufentanil into one nostril. If more than one dose was needed, then they were given into the alternate nostril.

And then the dose escalation is as follows:

Step I: A 9 mcg dose, which was repeated at 10 and 20 min if required and drowsiness scale evaluation was less than 2. If ineffective at 30 min, usual opioid breakthrough was given and Step II was followed for next episode.

Step II: 18 mcg dose, which may be repeated at 10 and 20 min if required and drowsiness scale evaluation was less than 2. If ineffective at 30 min, give usual opioid breakthrough and go to Step III for next episode. As for above

Step III: 36 mcg dose, which may be repeated at 10 and 20 min if required and drowsiness scale evaluation was less than 2. If ineffective at 30 min give usual opioid breakthrough and conclude study. As for above

Data was entered directly onto dedicated forms at 0, 5, 10, 15, 30, 60 and 120 min. Data collected included pain on a 0–10 VRS: 0 = no pain, 10 = worst possible pain, drowsiness on 0–4 scale: none (0, patient alert); mild (1, occasionally drowsy, easy to rouse); moderate (2, frequently drowsy, easy to rouse); severe (3, somnolent, difficult to rouse); unconscious (4, unrousable), respiratory rate (RR), oxygen saturations, presence or absence of nausea, vomiting or confusion, nasal pain or bleeding. Additionally, patients were asked after each episode of IN sufentanil whether this had provided worse, the same or better relief than their usual opioid breakthrough agent.

Ongoing phase

During the ongoing phase the titrated effective dose was used for all subsequent episodes of breakthrough pain. If IN sufentanil was effective, any patient later in the trial, who was discharged, was given the option of use at home...
with follow-up monitoring by a community palliative care service.

The outcomes measured were pain on a 0–10 VRS, the need to revert to the previous breakthrough after 30 min and the number of patients who chose to continue in the ongoing phase. The adverse effects recorded included drowsiness score 2 or greater, RR less than 10, a significant decrease on oxygen saturation (SPO$_2$ less than 90), nausea/vomiting, confusion, and nasal bleeding or pain.

The Friedman test was used to assess the statistical significance of change in VRS at 15 and 30 min.

### Results

Data was available for 30 patients who had 64 episodes (in total for both phases) of IN sufentanil. The range of primary malignancies was in line with those commonly represented in an inpatient palliative care unit with the most common cancers being colorectal, lung and breast. The most common types of pain mechanism for the breakthrough pain were neuropathic (11 patients), visceral (7 patients), somatic (6 patients), but also included mixed somatic/neuropathic (5 patients), and unknown mechanism in one patient. A variety of opioids were used for background and breakthrough analgesia (see Table 1) but morphine was the commonest in 43 and 60% of patients respectively.

The median VRS scores (mean, SD) were 5.5 (5.9 ± 1.8), 3 (3.3 ± 2.3), 2 (2.5 ± 2.4) at 0, 15 and 30 min respectively (Figure 1). There was a significant reduction in pain scores at 15 ($P < 0.0001$) and 30 minutes ($P < 0.0001$). If response to an analgesic is taken as a percentage pain intensity difference (PID%) ≥33%, then (at 30 min) 40 out of the 64 episodes (63%) could be counted as responding to the medication. The dose range for these responsive episodes was from 9 to 108 mcg, with 18 mcg being the median dose. The majority (63%) of these responsive episodes were well controlled by IN sufentanil 18 mcg (i.e. two sprays) or less.

Twenty-three of the patients rated the IN medication as better than their normal breakthrough medication. That only six patients continued the medication on discharge or at the end of the trial was due to decline in health status or patient death because of progression of the underlying cancer. Only in 4/64 episodes (6%) of use did the patient have to revert to their usual breakthrough after 30 min.

There was no correlation with patients’ 24 hr opioid dose or a patient’s usual opioid breakthrough, and the effective IN sufentanil dose. For example, there were two different patients, one on a usual breakthrough of morphine 40 mg s/c, the other on morphine 2.5 mg s/c, both achieved good pain relief at 15 min, after IN sufentanil 18 mcg with no adverse effects in either.

### Adverse events

Drowsiness with a score of 2 or greater occurred with three episodes of IN sufentanil. Nausea occurred in two uses of the medication, and headache in one. In one of the episodes of nausea this was associated with facial flushing and sweating. One trial was abandoned when a patient’s RR fell from 20 to 16, although the oxygen saturations were normal. This patient also experienced moderate drowsiness and the VRS decreased from 9 initially to 2 at 30 min.

Five patients withdrew from the trial – one due to headache associated with IN sufentanil; one due to severe osteoarthritis in both hands making it too difficult to use the PCINA device; one due to inadequate pain relief despite the maximum IN dose i.e. 108 mcg. (This patient went on to have a intrathecal infusion of morphine and bupivacaine); one due to a fall in RR from 20 to 16 (see above); and one patient discharged themselves against medical advice the day after the first IN administration.

### Discussion

Breakthrough pain continues to be a significant issue for palliative care cancer patients. What is required for breakthrough pain management is rapid onset, relatively short duration, intense analgesia.

This was an observational study that showed that IN sufentanil was of rapid onset, effective, safe and relatively user friendly in a range from 9–108 mcg (total dose). The effective dose in the majority (63%) of patients was 18 mcg.

<table>
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<th>Table 1 Opioid usage prior to IN sufentanil</th>
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Figure 1  Median pain VRS over time.

![Graph showing median pain VRS over time.](http://pmj.sagepub.com)
(i.e. 2 sprays) or less. As this was a novel technique and we had minimal data to guide us, we elected for an inpatient dose titration phase and to err on the side of safety, using frequent observations of RR, sedation scores and SPO2 so that any significant adverse effects would be detected and managed early. It turned out that we had been overly cautious, and there were no significant adverse effects, and no need for any acute interventions.

The PCINA GO Medical device is similar in design to the nasal sprays used to deliver nasal decongestants, but has important safety features, that is, the exact dose delivered is regulated, plus the possibility on an in-built lock out. We elected to use a no lockout device for two reasons:

1) the dose titration phase was doctor or nurse supervised, which imposed an effective lockout of 10 mins
2) we anticipated that more than one spray would be required, and once the dose had been determined, it would have been unreasonable to impose the standard 4 min lockout instead of letting patients use the spray to alternate nostrils at 2 min intervals to achieve this dose rapidly.

The devices are 5 or 10 ml bottles that are filled with the required analgesia, usually by a pharmacist. We elected to use sufentanil, which due to its favourable pharmokinetic properties, plus the availability of a suitable commercially available solution, appeared to us to be the most promising of the currently available opioids. Sufentanil is not routinely available in Australia, but is readily obtained through the Federal Government supervised Special Access Scheme (SAS). (Drugs on this scheme have not been approved by the Therapeutic Goods Administration, but are available on a case by case basis for patients who have a life threatening illness).

Transmucosal fentanyl citrate (OTFC) ACTIQ™ was not available in Australia when our trial started, but became available with limited access towards the end. It has now been added to our Pharmaceutical Benefits Scheme (a system which subsidises high cost medications). OTFC needs to be moved between the cheek and gum for 5 min. Streisand, et al.11 showed that with OTFC devices, an effective analgesic concentration is achieved in 15 min, lasts 1–2 hrs and the bioavailability is of the order of 50%. Portenoy, et al. reported on a successful dose titration trial of OTFC for breakthrough pain in domiciliary palliative care patients.12 Interestingly, no relationship was shown between the regular 24 hr opioid required or usual breakthrough dose and the OTFC dose required. It would appear however to be a better option in patients requiring a high opioid dose for adequate control of breakthrough pain. IN sufentanil at high doses (though these were very rarely needed) is pragmatically difficult. Patients are happy to use 1–4 sprays, that is, up to 36 mcgs but above this it is a bit cumbersome, and also the amount swallowed may be significant even if given over several minutes.

We acknowledge several limitations to this study. First, it is an open label observational non-blinded study, and as such potential bias in reporting of pain results, adverse effects and patient preferences are possible. Additionally, it was conducted only in inpatient palliative care units, although some patients continued the use of the medication at home. However, as explained above, these limitations were essentially unavoidable given the lack of safety data available prior to this trial. Additionally, IN sufentanil does not come pre-packaged, and therefore requires the contents of a commercially available sufentanil ampoule to be emptied into the PCINA bottle, usually in a pharmacy.

Conclusion

Breakthrough pain in palliative care continues to be a difficult area to provide effective analgesia. The results of this study show that the IN route is a practical alternative to oral, subcutaneous and intravenous administration of medication for breakthrough pain. It provides acceptable and often preferred breakthrough analgesia for many patients and most importantly, it can provide rapid pain relief. This study also showed that IN sufentanil can be used safely, with a very low incidence of adverse effects, in an inpatient palliative care population. We suggest that IN sufentanil be added to the armamentarium of medication used to treat breakthrough pain with the proviso that it requires an initial dose titration phase, similar to that recommended when using ACTIQ lozenges.

References


Chapter Eleven

The compatibility and stability of midazolam and dexamethasone in infusion solutions

Chapter Eleven is published as:
Introduction

In Palliative Care it is common to use of syringe drivers to deliver a mix of medications via a continuous subcutaneous infusion. Despite this widespread practice, there have been very few studies examining the stability and compatibility of medications mixed together. To try and improve the available evidence for this practice, two studies were done - one looking specifically at the combination of midazolam and dexamethasone and a second study examining the effect of PVC tubing on loss of clonazepam.

This chapter is an important study that assessed the effects of different medications when mixed in solution, a very common route of administration of drugs in Palliative Care. It showed that if these two medications are mixed, then the levels of activity of midazolam decrease substantially. Perhaps more importantly it showed that even when there is no visual incompatibility, there can be drug loss, in infusion solutions. It had been common practice in Palliative Care to simply rely on whether cloudiness occurred on mixing two solutions (visual incompatibility).
The Compatibility and Stability of Midazolam and Dexamethasone in Infusion Solutions

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Abstract
The delivery of subcutaneous medication by continuous infusion is common in palliative medicine. Many centers combine multipal medications, but the analytical confirmation of the compatibility and stability of these combinations has rarely been performed. This study examined the compatibility and stability of midazolam and dexamethasone using high performance liquid chromatography. Nine different solutions were prepared in polypropylene syringes by combining these two drugs with 0.9% sodium chloride. When these two drugs were combined in a syringe, there was significant loss of midazolam over 48 hours, with only 60–80% of the initial concentration remaining in syringes stored at 35–39°C. This study demonstrates that cloudiness of a solution is not the only predictor of drug loss and that drug loss may occur even in solutions that remain clear at time of preparation. The clinical implications of these results are that dexamethasone and midazolam should not be combined in syringe driver solutions.

Key Words
Parenteral infusions, subcutaneous injection, midazolam, dexamethasone, drug compatibility, drug stability, syringes, palliative care

Introduction
Subcutaneous administration of medication using syringe drivers is a commonly used alternative route of administration in palliative care patients who can no longer tolerate oral medication or when absorption in the gut is questioned. Opioids are frequently used in combination with other drugs. Some centers combine up to six medications in the one syringe. The compatibility and efficacy of such combinations in syringe pumps is assumed, but often has not been scientifically validated. Two such drugs used in combination are dexamethasone and midazolam.

Dexamethasone is an agent used for nausea and vomiting, raised intracranial pressure, anorexia/cachexia syndrome, pain, and spinal cord compression. It has a long half-life, but is sometimes used in subcutaneous infusions where the patient is no longer able to tolerate oral medication. Midazolam is used for anxiety, delirium, agitation, seizures, myoclonic jerks, and in situations where rapidly acting sedation medications are combined without opioids.
is needed (e.g., catastrophic hemorrhage). It has a short onset of action and a short half-life. Its long-term use may be limited by tolerance. Midazolam and dexamethasone may be combined in situations where anxiety and pain are prevalent. The stability and compatibility of the combination is unknown, with some reports suggesting visual incompatibility and others suggesting visual compatibility. The aim of this study was to investigate the stability and compatibility of dexamethasone and midazolam combined in infusion solutions.

Methods
Reagents
The reagents used were ampoules of dexamethasone sodium phosphate (David Bull laboratories, Mulgrave North, Victoria, Australia) equivalent to 4 mg/mL and pure dexamethasone disodium phosphate (Sigma Chemicals Co. St Louis MO, USA); ampoules of midazolam hydrochloride 5 mg/mL (Hypnovel) and pure midazolam hydrochloride (Roche Products Pty Ltd, Dee Why, New South Wales, Australia); sodium chloride for injection 0.9% B.P. (Pharmacia and Upjohn, Bentley, Western Australia, Australia); disodium hydrogen phosphate AR grade (Prolabo, Manchester, UK), and sodium dihydrogen phosphate AR grade (Prolabo, Manchester, UK). Water used in preparing solutions was purified by nanopure reverse osmosis and filtration unit. Acetonitrile and methanol were HPLC grade (Mallinckrodt Pty. Ltd., Phillipsburg, NJ).

Experimental Design
Infusion solutions, equivalent to those used in 24-hour infusion pumps, were prepared in polypropylene syringes (Terumo, Aust. Pty. Ltd., North Ryde, Sydney, Australia). The syringes were sealed by luer lock combistopper caps (Braun, Germany). The contents of the dexamethasone and midazolam ampoules were transferred into 10 mL syringes and made up to a volume of 8 mL, with 0.9% sodium chloride solution. Only solutions that remained clear on preparation were analyzed. Nine different solutions were analyzed (Table 1). Four syringes of each solution were prepared, with two being stored at room temperature (22–26°C) and two placed in an oven at 37°C (35–39°C). Syringes at room temperature were not shielded from light. Concentrations of dexamethasone and midazolam were determined on day of preparation and at 24 hours and 48 hours after preparation. At each point, solutions were examined for any volume loss, development of color, or precipitate. The pH was measured on the first day and at 48 hours.

Analytical Method
Midazolam and dexamethasone concentrations were determined by high performance liquid chromatography (HPLC). Chromatography was performed using a M717 autosampler in conjunction with a M510 solvent delivery system and an 8 × 10 radial compression module with a 4 µm Nova-Pak C18 cartridge (Waters Corporation, Milford, MA). A UV-480 detector model (Waters Corporation) was used. The mobile phase consisted of methanol, acetonitrile, and sodium phosphate buffer (0.025M, pH 6.3), combined in proportions of 100:100:170. The sodium phosphate buffer was prepared by mixing 0.025M NaH₂PO₄ and Na₂HPO₄ solution in proportion of 4:1. The mobile phase was pumped through the system at a flow rate of 1.9 mL/min, with a wavelength of detection set at 254 nm.

Samples were prepared by taking 50 µL of infusion solution and diluting with 4 mL of mobile phase containing 0.05% bupivacaine hydrochloride (Astra Pty. Ltd., Ryde, New South Wales, Australia) as the internal standard. Samples were thoroughly mixed and 50 µL of this solution was injected into the HPLC system. Interpretation of the chromatographic peaks was performed using Maxima data acquisition software (Waters Corporation). Standard solutions of midazolam HCl and dexamethasone disodium phosphate were prepared from pure powder forms of the drugs and ranged from 0.1 mg/mL to 1 mg/mL. Quality control (QC) solutions of both dexamethasone and midazolam were also prepared using commercially available ampoules of each drug. The intended final concentrations of the QC samples for midazolam and dexamethasone were 0.4 mg/mL, 0.8 mg/mL, and 1.0 mg/mL, 0.5 mg/mL, respectively. Each analytical run incorporated four midazolam standards, four dexamethasone standards, and two QC samples for each drug. Syringe samples were analyzed in duplicate.

Retention times of midazolam, dexamethasone, and bupivacaine were 10.5–12.5 minutes.
1.6–1.8 minutes and 16–18 minutes, respectively. Calibration curves for midazolam and dexamethasone were linear and coefficients of determination ($r^2$) were all greater than 0.999. Reproducibility of both between and within assay reproducibility was assessed by five replicates of each QC in five successive assays. These were analyzed by two-way analysis of variance. The within-assay coefficient of variance (CV) for all QCs was less than 2.5% and the between-assay variance was less than 2.5%. Degradation studies were performed to ensure that the breakdown products of dexamethasone and midazolam did not interfere with the assay.

### Statistical Evaluation of Data

Samples prepared in duplicate gave results within 5% of their mean, and statistical analysis was performed on the mean value of these duplicates. For each of the solutions prepared, a two-way analysis of variance (with replicates, to account for duplicate syringes) was used to determine whether significant variance occurred which could be due to the effects of temperature or time and whether any significant interaction (temperature x time) of the sources of variance existed. The degrees of freedom for these three parameters and the total degrees of freedom were 1, 2, 2, and 11, respectively.

### Results

Results obtained from the analyzed samples are shown in Table 1. The values are the percentage of the initial midazolam or dexamethasone concentration at 24 and 48 hours following syringe preparation. All combinations in Table 1 were analyzed by two-way analysis of variance with replicates to account for duplicate syringes.
remained clear at time of preparation. Concentrations measured for midazolam and dexamethasone in syringes at time of preparation were within 5–7.5% of the target value. Combinations containing higher concentrations of midazolam and dexamethasone (e.g., midazolam 7.5 mg + dexamethasone 4 mg in 8 mL, and midazolam 5 mg + dexamethasone 4 mg in 8 mL) were cloudy when prepared and were not analyzed.

In all solutions containing midazolam and dexamethasone, there were significant differences in the concentration of midazolam. This included temperature-dependent ($F = 11.92$–$15.41$, $P < 0.01$ to $P < 0.05$) and time-dependent effects ($F = 7.66$–$273.25$, $P < 0.0001$ to $P < 0.05$).

For solutions containing only midazolam there was no significant difference attributable to time or temperature. In regard to the two solutions containing dexamethasone only, solution 5 showed a significant time dependent effect ($F = 9.16$, $P < 0.05$).

When dexamethasone was combined with midazolam, only solution 6 showed a significant variance in concentration for dexamethasone, with both a temperature-dependent ($F = 10.25$, $P < 0.05$) and time-dependent effect ($F = 8.57$, $P < 0.05$) observed.

Visual inspection of all syringes at each time point revealed crystallization in the first two replicates of solution 9 stored at 37°C. Crystallization appeared in one syringe at 24 hours and in both syringes at 48 hours. When analyzed, only 30.9% of midazolam remained at 48 hours. Because of the variability in the time of appearance of crystallization and the very small amount of crystallization observed, a further four replicate syringes were prepared for this combination and analyzed. These replicate syringes produced no visible crystallization, but significant loss of midazolam at 48 hours was still observed ($F = 37.6$, $P < 0.05$). At 48 hours, only 80% of the original concentration of midazolam remained. The pH of the analyzed solutions did not alter appreciably over the 48 hours.

**Discussion**

The appearance of cloudiness when two drugs are mixed may indicate that a chemical incompatibility is occurring. In this study, when midazolam and dexamethasone were mixed at concentrations equal to or higher than 0.625 mg/mL (or 5 mg/8 mL) and 0.5 mg/mL (4 mg/8 mL) respectively, cloudy solutions resulted even when dexamethasone was added last after dilution of midazolam with the diluent to the final volume minus the volume of the dexamethasone to be added. This visual incompatibility is thought to be due to a pH effect, as the open-ring and closed-ring forms of the midazolam molecule exist in a pH dependent equilibrium. At the pH of midazolam ampoules (pH 3.5), the open-ring form, which is more hydrophilic, predominates. At higher pH values, the closed-ring (more lipophilic) structure predominates. Addition of dexamethasone injection (pH 7) will result in an increase in pH and more of the midazolam will be present in the lipophilic form, resulting in reduced solubility and possible precipitation, resulting in a cloudy solution. However, some combinations do remain clear, despite the increase in pH from addition of dexamethasone.

In clinical practice it is assumed that the potency of midazolam is maintained in these solutions as long as they remain clear. The results of this study show that even in those solutions which remain clear, there is still significant loss. At 24 hours, the syringes containing midazolam and dexamethasone which were stored at 37°C had a 16–27% reduction in midazolam concentration. By 48 hours, the concentration was reduced by up to 40%. This is an important finding, as most mixing occurs at room temperature and then the syringe in the respective driver is worn close to a patient and may reach a temperature closer to 37°C than room temperature.

As shown previously, this study found that solutions of midazolam alone were stable over 48 hours.

Although statistically significant differences were reported for dexamethasone in solutions 5 and 6, the differences observed are no more than 6% of the initial concentration and may represent experimental error or a combination of a small clinically insignificant loss and experimental error. In the clinical situation, it is generally accepted that a difference of less than 10% is not significant.

The implications of this study for clinical practice are twofold. First, it shows that drug loss may occur even if there is no cloudiness or crystallization in the solution. If a combination of midazolam and dexamethasone must be
used as no alternatives are available, the solutions should be prepared every 24 hours to minimize midazolam loss, and the syringe driver should be placed to minimize warming of the solution. Clinicians should be aware that there may be significant loss of midazolam with a small increase in temperature of the solutions. Based on this finding, it is recommended that, whenever possible, combinations of midazolam and dexamethasone in the same syringe should be avoided.

References


Chapter Twelve

Effect of Tubing on Loss of Clonazepam Administered by Continuous Subcutaneous Infusion

Chapter Eleven is published as:
Introduction

The article in this chapter was the first study to show that there is significant loss of clonazepam, when infused through PVC tubing, but not through non PVC tubing.
Original Article

Effect of Tubing on Loss of Clonazepam Administered by Continuous Subcutaneous Infusion

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Abstract

Previous studies have reported loss of clonazepam from solutions administered intravenously from plastic infusion bags and administration sets. In palliative care, clonazepam is sometimes administered through syringe drivers using polyvinyl chloride (PVC) infusion tubing. No data currently exist to show whether use of PVC tubing affects the amount of clonazepam actually received by the patient. This study compared the use of two different types of PVC tubing with a non-PVC tubing. Solutions containing clonazepam or clonazepam and morphine were prepared with either normal saline or water for injection as diluent. Concentrations of morphine and clonazepam were determined using high-performance liquid chromatography. Significant loss of clonazepam (up to 50%) was observed in all solutions infused through PVC tubing. Solutions infused through non-PVC tubing retained greater than 90% of the initial concentration of clonazepam. It is recommended that when administering clonazepam using a syringe driver, non-PVC tubing be used.

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Key Words

Subcutaneous drug administration, clonazepam, morphine sulfate, palliative care, stability, sorption

Introduction

Clonazepam, a benzodiazepine, is used in palliative care for its anxiolytic effect, anticonvulsant activity, and analgesic effects in neuropathic pain. It can be given orally or administered as a subcutaneous bolus or as a 24-hour continuous subcutaneous infusion using a syringe driver or a similar device. When preparing clonazepam for infusion, diluents such as sodium chloride 0.9% or water for injection are added. On occasion, other medications, such as morphine, may also be present in the infusion solution. These solutions, prepared in polypropylene syringes, are slowly administered over 24 hours through...
infusion tubing. Different types of infusion tubing are used, some of which are made of polyvinyl chloride (PVC).

Sorption (loss) of benzodiazepines to PVC bags and tubing has been reported in intravenous (IV) solutions of clonazepam administered over a few hours.\(^2,3\) Loss of clonazepam into IV tubing has been reported to be concentration and flow dependent, with use of polyethylene-coated tubing resulting in no loss of clonazepam.\(^3\) Concentrations, volumes, and flow rates used in the studies cited above differ considerably from those commonly used in palliative care. Data on the effect of tubing or presence of another drug on clonazepam administered using a syringe driver have not been reported in the literature.

The aim of this study was to investigate whether significant loss of clonazepam occurred when clonazepam was delivered through different types of tubing over 24 hours using a syringe driver. The effect of diluent, drug concentration, and presence of morphine was also investigated.

**Methods**

**Reagents**

The reagents used were ampules of clonazepam (1 mg/mL); pure clonazepam powder (Roche Products Pty. Ltd., Dee Why, New South Wales, Australia); ampules of morphine sulfate and pure morphine sulfate powder (David Bull Laboratories Pty. Ltd., Mulgrave, Victoria, Australia); nalorphine hydrobromide B.P. (Wellcome Foundation Ltd., London, UK); sodium chloride injection 0.9% and water for injection (Pharmacia West Ryde, Australia); disodium hydrogen orthophosphate and sodium dihydrogen orthophosphate (AR, Sigma Chemical Co., St. Louis, MO, USA); and acetonitrile and methanol (ChromAR HPLC, Mallinckrodt, Clayton South Australia Pty. Ltd.). Water used in preparation of solutions was purified using a Millipore reverse osmosis and filtration system (North Ryde, NSW, Australia).

**Experimental Design**

Eight different solutions containing clonazepam either alone or in combination with morphine were prepared as outlined in Table 1. For each solution, 10 replicates were prepared.
in glass beakers. Duplicate samples for high-performance liquid chromatography (HPLC) analysis (50 μL) were withdrawn from each beaker. Two of the replicates were transferred to amber 20 mL glass bottles and sealed. These were then stored at room temperature for 24 hours. Two replicates were transferred to 30 mL polypropylene syringes (Terumo, Australia) and sealed with luer-lock stoppers (Combi-stopper, Braun, Bella Vista, NSW, Australia) and stored at room temperature. The remaining six replicates were each transferred into polypropylene syringes (Terumo, Australia) and connected to Graseby MS16A syringe drivers (Smith’s Medical Australasia, Bundall, Qld., Australia) set to run over 24 hours. Of the six replicates connected to a syringe driver, two were attached to 75 cm length PVC tubing (Tuta Laboratories, Australia) (PVC1), two were attached to 150 cm length non-PVC tubing (IVAC, San Diego, CA). A 26-gauge needle was attached to the end of each tubing, and the needle was inserted into a capped 20 mL amber glass bottle. The solutions were pumped through this tubing over 24 hours at room temperature, with the eluant being collected in the sealed glass 20 mL amber bottles. At 24 hours, samples (50 μL) were withdrawn from the stored glass bottles, stored polypropylene syringes, and bottles containing the eluant from each of the Graseby infusion driver setups.

**Analytical Method**

HPLC was used to determine the concentrations of clonazepam and morphine sulfate. Chromatography equipment consisted of an M717 autosampler in conjunction with an M510 delivery system, a 8 × 10 radial compression module with a 4 μm NovaPak C18 cartridge and a 490E UV detector (Waters Corporation, Rydalmere, NSW, Australia). The mobile phase consisted of acetonitrile, methanol, and sodium phosphate buffer (0.025 M, pH 5.5) combined in the proportions 100:100:170. The sodium phosphate buffer (0.025 M, pH 5.5) was prepared with 0.025 M sodium dihydrogen orthophosphate (400 mL) mixed with 0.025 M disodium hydrogen phosphate solution (100 mL). Chromatography was performed using a flow rate of 0.9 mL/min with detection of the analytes and internal standard at a wavelength of 280 nm. Injections of 50 μL were made and chromatographic peak integration was performed using Maxima data acquisition data software (Waters Corporation).

Standards of clonazepam ranged from 0.5 to 0.05 mg/mL. Standard solutions of morphine sulfate ranged from 10 to 1 mg/mL. An internal standard solution (nalorphine hydrobromide 0.05 mg/mL) was prepared prior to each assay by dilution of the stock solution (1 mg/mL) in mobile phase.

Quality control (QC) solutions were prepared prior to each assay in a manner intended to reflect the method by which the sample infusion solutions were prepared. This involved transferring the contents of commercially available ampules into volumetric flasks and diluting to the required volume. The intended final QC concentrations for clonazepam were 0.4 and 0.1 mg/mL. For morphine sulfate, the intended final QC concentrations were 6 and 3 mg/mL. Aliquots (50 μL) taken from each solution were transferred to a 10 mL glass tube, and 2 mL of internal standard solution was added. Samples were then thoroughly mixed with a vortex mixer. Each analytical run incorporated four clonazepam standards, four morphine sulfate standards, two QC samples for clonazepam, and two QC samples for morphine sulfate. The retention times for morphine sulfate, clonazepam, and internal standard (nalorphine) were 4.0, 6.0, and 9.0 min, respectively. Calibration curves for both morphine sulfate and clonazepam were based on peak height ratios of clonazepam or morphine sulfate to nalorphine ratio. Calibration curves for both clonazepam and morphine sulfate were linear over the range examined, and coefficients of determination (r²) were consistently greater than 0.995. Between- and within-assay reproducibility were assessed by quantifying four replicates of each QC on five successive assays. When analyzed by two-way analysis of variance (ANOVA), the within-assay coefficient of variation (CV) for all QCs was less than 1.9%. Between-assay CVs were less than 1.8%. The mean values of all QCs were within 3% of nominal concentrations.

The stability-indicating capacity of the assay was determined using forced degradation of morphine and clonazepam under extremes of
pH and temperature. A decrease in the peak heights of clonazepam and morphine was observed, and no interfering peaks were observed.

Statistical Evaluation of Data

Samples prepared in duplicate for injection gave results consistently within 5% of their mean. Data analysis was performed on the mean values of these duplicates. For each solution, a one-way ANOVA was performed to determine whether significant variance occurred that could be attributed to the effects of the treatment. When a significant difference was observed, Tukey’s multiple range test was used to determine which treatments were significantly different.
**Results**

The drug concentration at 24 hours was divided by the initial concentration (at time of preparation) to produce the percentage of initial concentration shown in Fig. 1. For all solutions prepared and stored in either a glass bottle or a syringe, concentrations at 24 hours were over 90% of the initial concentration. Solutions pumped through non-PVC tubing also produced concentrations that were over 90% of the initial concentration. This treatment was not significantly different from storage in a syringe (Tukey test, \( P > 0.05 \)). Solutions pumped through PVC tubing exhibited significant loss of clonazepam (ANOVA \( F > 50; P < 0.05 \)). No significant loss of morphine was observed in any of the solutions. Significant loss of clonazepam occurred in solutions with and without the presence of morphine when pumped through PVC tubing. Choice of diluent did not affect the significant loss of clonazepam observed with PVC tubing as shown in Fig. 1.

**Discussion**

The results of this study clearly indicate that there is significant loss of clonazepam when it is infused from syringe drivers through PVC tubing. This significant loss does not occur when solutions are infused through non-PVC tubing. Length of tubing affects the amount lost, with greater loss observed in the 150 cm tubing (PVC2) than in the 75 cm tubing (PVC1). In the clinical situation, the amount lost will be significant. In the case of PVC2 tubing, when administering 2 mg of clonazepam over 24 hours, only 50% of the dose will be delivered. The major factor affecting loss of clonazepam was the type of tubing used and not the presence of another drug or the diluent used. There appears to be a concentration-dependent effect on the proportion of clonazepam lost after infusion through PVC tubing. When 4 mg of clonazepam was administered over 24 hours, the percentage loss (approximately 25%) was lower than that at 2 mg (approximately 50%). This loss is still significant, with at least 25% of the dose (or 1 mg) not being administered.

Based on this study, it is recommended that when clonazepam is to be administered clinically using a syringe driver, non-PVC tubing should always be used to ensure that the desired dose is delivered over the time of infusion.

**References**

Chapter Thirteen

Effects of opioids and sedatives on survival in an Australian inpatient palliative care population

Chapter Thirteen is published as:
Introduction

As stated in the introduction to the article there seems to be a “perception in medicine and the wider community that symptom control in Palliative Care is associated with the hastening of death”. This is particularly associated with opioids and sedatives and is justified in medical ethics and medical codes of conduct via the “Doctrine of Double Effect”. This article was seeking to study what, if any, association there was between opioid and sedative use and timing of death, relative to admission to an inpatient Palliative Care unit.

This was the first Australian study to look at the association between medication usage (specifically opioids and sedatives used in the last 24 hours of life) and time from admission to death in a Palliative Care setting. It found there was no association between the use of opioids and sedatives, and time (or ‘survival’) in an inpatient Palliative Care unit.
ORIGINAL ARTICLE

Effects of opioids and sedatives on survival in an Australian inpatient palliative care population

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Abstract

Aims: To assess whether opioid and sedative medication use affects survival (from hospice admission to death) of patients in an Australian inpatient palliative care unit.

Background: Retrospective audit. Newcastle Mercy Hospice – a tertiary referral palliative care unit. All patients who died in the hospice between 1 February and 31 December 2000.

Methods: Length of survival from hospice admission to death, and the median and mean doses of opioids and sedatives used in the last 24 h of life. Comparison of these with published studies outside of Australia.

Results: In this study, the use of opioids, benzodiazepines and haloperidol did not have an association with shortened survival and the only statistical significant finding was an increased survival in patients who were on 300 mg/day or more of oral morphine equivalent (OME). The proportion of patients requiring greater than or equal to 300 mg OME/day (at 28%) was higher than published studies, but the mean dose of 371 mg OME/day was within the range of other studies. The proportion of patients receiving sedatives (94%) was higher than other studies, but the median dose of parenteral midazolam equivalent of 12.5 mg per 24 h was lower than other studies from outside Australia.

Conclusions: There was no association between the doses of opioids and sedatives on the last day of life and survival (from hospice admission to death) in this population of palliative care patients. (Intern Med J 2005; 35: 512–517)

Keywords: palliative care, survival analysis, narcotics/therapeutic use, hypnotics and sedatives/therapeutic use, double effect.

INTRODUCTION

There is a perception in medicine and the wider community that symptom control in palliative care is associated with the hastening of death. This seems mainly based on the idea that morphine in particular, and more recently sedative medications, relieves symptoms but leads to a premature death. Some commentators have dubbed this ‘slow euthanasia’, whilst others have been critical of this term and thinking. The idea that symptom control may be associated with hastening death is a common feature of codes of ethics of different medical organizations. For example, the Australian Medical Association states that terminally ill patients have the right ‘to receive treatment for pain and suffering, even when such therapy may shorten a patient’s life’. This thinking is based on the ethical concept of the principle of double-effect. This so called double-effect reasoning has been initially attributed to Thomas Aquinas (in relation to self-defence) and more recently developed by others. The conditions of this principle that must be met in relation to medical treatment are:

- The treatment must have potential beneficial and harmful effects
- The clinician intends the beneficial effect (relief of symptoms), but the foreseen harmful effect (hastening death) may be unavoidable
- The harmful effect (death) is not necessary to achieve the beneficial effect (relief of symptoms)
- The beneficial effect must outweigh the harmful effect (i.e. the relief of suffering is a compelling reason to justify the risk of the harmful effect)

Questioning of the use of this ethical principle has occurred, based on a clinician’s intentions. However, more recent studies have looked at the question of whether the idea of hastened death with opioid/sedative use is clinically correct.

There have been previous studies from Japan, England and Israel that have looked at opioid use and survival from time of admission to a hospital or palliative care unit to death. None has shown that opioid usage influences survival. All have had a different methodology, with some looking at different levels of morphine use and survival. Others like Thorns and Sykes have looked at the change in morphine dosage and survival, based on the idea that the rate of change in

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Potential conflicts of interest: None
dosage may be a more important factor than total dose. They found that survival was not related to the rate of increase in dose, and that a large increase in the dose of opioids was not more likely to occur in the last 48 h of a patient’s life.12

Studies have been performed in Japan,11 England,9,14 Germany,15 Italy16 and Taiwan17 looking at sedative use and survival in terms of time from admission (to an outpatient palliative care programme or an inpatient facility) till death. Again all have had a different methodology and none has shown an influence of sedative use on survival.

The use of sedatives as opposed to the practice of sedation has been much talked about in the literature. Midazolam and haloperidol are the most commonly used sedative medications in palliative care.9 Benzodiazepines are used to treat anxiety, nausea and vomiting, delirium, seizures, myoclonus and dyspnœa, whereas haloperidol is most commonly used to treat delirium (including terminal agitation), nausea and vomiting.19,20

The other use of sedative medications is as part of a regime to treat symptoms that are refractory to standard palliative treatments. Morita et al. have defined this as ‘the use of sedative medications to relieve intolerable and refractory distress by the reduction in patient consciousness’.21 It is difficult in reviewing studies, looking at sedative use, to define clearly and objectively whether the use was as part of standard symptom control or as part of treatment of refractory symptoms. This may be a result of retrospective studies or that there is a continuum between the two. The other controversy about sedative use has been the variation of doses used according to different countries. This was highlighted in a multicentre international study looking at ‘sedation for uncontrolled symptoms in terminally ill patients’.22 The median dose of midazolam used varied between 15 mg/day (Israel and South Africa) to 52 mg/day in Spain. The reasons for the variation are unclear but the authors suggested differences in culture, truth-telling and previous benzodiazepine exposure.

It is unclear where the practice of Australian palliative care falls in the use of opioids and sedatives, and whether their use has any effect on survival of terminally ill patients. A small study has looked at 50 patients in regards to dignity in dying, and found that 88% of patients used benzodiazepines in the last 3 days of life (total dosage of midazolam varied from 2.5 to 47 mg in those last 3 days), 86% of patients used opioids with a mean daily dose of 198.6 mg of oral morphine equivalent (OME)/day.23 However, that study did not look at survival with regards to opioid and sedative use. Therefore, this present study was carried out with the aims of recording the median dosage of opioids and sedatives used in the last 24 h of life; examining whether there is any effect on survival in the hospice according to different doses of opioids or sedatives; and to compare these results to previously published international studies, performed with a similar methodology.11,13

This present study was a retrospective review of use of opioids and sedatives in the last 24 h of life. The retrospective nature of this review ensured that no bias was able to occur due to doctors knowing about the study and possibly changing their practice. The patients were in the Newcastle Mercy Hospice, a 20-bed freestanding building on the same grounds as the Newcastle Mater Misericordiae hospital. The hospital is the main cancer referral centre for the Hunter region of New South Wales. The Hunter region has a population of approximately 540 000 people. The Newcastle Mercy Hospice is the inpatient unit of the Newcastle palliative care service. This is an integrated service consisting of inpatient beds, community care and consultation service. A previous study has described the characteristics of patients on the service and found the median survival was 54 days (from the time of referral till death).24 Patients can be referred to the inpatient hospice for admission if they are on any of the Hunter Area palliative care services, have the consent of their general practitioner or specialist, and fit the hospice criteria of admission for symptom control, terminal care or respite. The medical practitioners who work in the hospice include three palliative care specialists who rotate through the hospice, supported by junior medical staff consisting of one registrar level and one senior resident medical officer level during the time of this study. Further after hours assistance is provided by general practitioners who have a special interest in palliative care.

METHODS

The medical record and medication charts of hospice patients were reviewed for all deaths between 1 February and 31 December 2000. During this period there were 545 admission to the hospice, with 232 deaths; medical records could only be obtained for 229 patients. No record was made of the intent of the use of sedative medication, as the intention was not clear from review of the records – this study simply looked at the doses recorded and the survival of the patient.

Opioid dosages were converted to their OME for comparisons.25 Benzodiazepines were converted to parenteral midazolam equivalent (PME) using parenteral midazolam 5 mg = diazepam 5 mg, and following a published table.26

The patients were then split into groups according to the respective PME and OME. Groupings chosen were based on previous studies in this area. The first grouping for PME was (<10 mg, >10 mg) as determined by Sykes and Thorns,27 and the second as defined by Morita et al. was 0 (not used), 1 (0.5–29.5 mg PME/24 h) and 2 (≥30 mg PME/24 h).11 OME was stratified to: 0 (<120 mg OME/24 h), 1 (120–299.5 mg OME/24 h) and 2 (≥300 mg OME/24 h).11,13

Using these groupings, the patients were compared for length of stay in the hospice (admission to death). The use of haloperidol was reviewed as well. Survival curves were calculated by the Kaplan–Meier method, with the log rank test used to compare groups. The P-values found in the calculations are on the survival curves (Figs 1,2). Statistical analysis was performed using StatsDirect software (Version 2.3.8; StatsDirect Ltd, Sale, UK).
RESULTS

Demographics
The median age of death was 72 years. The median length of stay (admission till death) in the hospice was 8 days. The median time from referral, to the palliative care programmes, until death was 57 days in the Newcastle service. The male : female ratio was 59:41 for the hospice.

The most common diagnoses of patients who died in the hospice were: lung (20%), colorectal (12%), gastroesophageal (10%), prostate (9%) and breast (8%) cancer.

Medications
Opioids were used most frequently, closely followed by benzodiazepines, with haloperidol used at a much lower frequency (Table 1).

Opioid doses were divided into three different groups according to the previous study carried out by Morita et al.11 (Table 2). Opioids administered were: codeine (n = 1 patient), fentanyl (50), sufentanil (3), hydromorphone (1), morphine subcutaneous (184), oral morphine (29), oxycodone (1) and pethidine (1).

Benzodiazepine doses were divided in two different ways (Table 2). There was no significant difference between these groups in relation to survival ($P = 0.45$, log–rank test (Sykes categories) and $P = 0.30$, log–rank test (Morita categories)).

Haloperidol usage is shown in Table 1. This was divided simply according to non-used or any dose used. There was no significant difference in survival between these two groups ($P = 0.90$, log–rank test).

The survival curves according to the different categories are shown in Figures 1 and 2.

The only significant finding was with the OME and the finding that those patients on $\geq 300$ mg/day had a longer survival time (from hospice admission to death), compared to patients on 120–299 mg/day and those on less than 120 mg/day ($P = 0.01$, log–rank test).

Tables 3 and 4 show a comparison of results of this study to previously published international studies.

DISCUSSION

This present study looked at the survival (from the time of hospice admission to death) in patients on opioids and sedatives in the last 24 h of life.

The use of opioids, benzodiazepines and haloperidol did not have an association with shortened survival and this is similar to other previous studies.11–17,27,28 The only statistical significant finding was an increased survival in patients who were on $\geq 300$ mg/day OME. The reasons why this group had a longer survival are unclear from this study. The most likely reason is that this group of patients represents a group of complex pain syndromes and as a result was admitted to the hospice earlier, needing higher doses of opioids to control their symptoms. The other possibilities are that this group of

Table 1 Opioids and sedatives in the last 24 h

<table>
<thead>
<tr>
<th></th>
<th>Frequency (n (%))</th>
<th>Mean dose (mg/24 h) (95%CI)</th>
<th>Median dose (mg/24 h)</th>
<th>Range (mg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (OME)</td>
<td>222 (97)</td>
<td>370.7 (287.4–454)</td>
<td>135</td>
<td>2–4710</td>
</tr>
<tr>
<td>Benzodiazepines (PME)</td>
<td>215 (94)</td>
<td>21.9 (18.2–25.6)</td>
<td>12.5</td>
<td>1–250</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>82 (36)</td>
<td>3.2 (2.9–4.3)</td>
<td>2.5</td>
<td>0.2–15</td>
</tr>
</tbody>
</table>

OME, oral morphine equivalent; PME, parenteral midazolam equivalent.
patients lived longer – directly as the result of higher opioid dosage, or from better pain control as a result of opioid use.

The proportion of patients requiring greater than or equal to 300 mg OME/day was higher in this present study (28%) than two previously published studies (12.1%,13 7.7%11). However, the mean dose of 370.7 mg OME/day is within the range of other studies of morphine use before death, i.e. 167 mg to 1977 mg OME/day.12,23,28–32 Whilst the median doses are shown in Table 4, mean doses are more commonly reported in published studies. Again these patients probably represent a group of complex pain syndromes for which patients are commonly admitted to our inpatient unit. The hospice is the only tertiary referral palliative care unit for a large population and large area in New South Wales, and as such is the likely place where the most complex symptomatology is seen amongst mainly oncological patients. This service also has a comprehensive community component and this means that patients are not generally admitted to the hospice unless their symptoms are difficult or complex.

The proportion of patients receiving sedatives (94%) is higher than the 1–88% found in a recent review of sedative use at the end of life.9 Interestingly, the study where 88% of patients used benzodiazepines was also carried out in Australia.23 The median dose of PME of 12.5 mg per 24 h is lower than most previously published studies (15–53 mg/24 h PME11,22,27,33). The increased frequency, but lower median dosages, suggests

### Table 2  Oral morphine equivalent and parenteral midazolam equivalent

<table>
<thead>
<tr>
<th>OME/24 h</th>
<th>n (%)</th>
<th>Median survival (days)</th>
<th>Mean survival (95%CI) (days)</th>
<th>Range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120 mg</td>
<td>106 (46)</td>
<td>7</td>
<td>11.4 (8.6–14.2)</td>
<td>0–91</td>
</tr>
<tr>
<td>120–299 mg</td>
<td>60 (26)</td>
<td>8</td>
<td>12.7 (9.3–16)</td>
<td>1–69</td>
</tr>
<tr>
<td>&gt;300 mg</td>
<td>63 (28)</td>
<td>16</td>
<td>18.3 (14–22.6)</td>
<td>0–103</td>
</tr>
<tr>
<td>PME/24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 mg</td>
<td>14 (6)</td>
<td>7</td>
<td>11.9 (4.7–19.0)</td>
<td>1–49</td>
</tr>
<tr>
<td>&gt;0 and &lt;30 mg</td>
<td>163 (71)</td>
<td>8</td>
<td>12.9 (10.6–15.3)</td>
<td>0–91</td>
</tr>
<tr>
<td>≥30 mg</td>
<td>52 (23)</td>
<td>11</td>
<td>16.6 (12.0–21.2)</td>
<td>1–103</td>
</tr>
<tr>
<td>≤10 mg</td>
<td>108 (47)</td>
<td>8</td>
<td>13.0 (10.0–16.1)</td>
<td>0–91</td>
</tr>
<tr>
<td>&gt;10 mg</td>
<td>121 (53)</td>
<td>9</td>
<td>14.3 (11.6–16.9)</td>
<td>0–103</td>
</tr>
</tbody>
</table>

OME, oral morphine equivalent; PME, parenteral midazolam equivalent.

### Table 3  Comparative frequency of medication use

<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequency (%)</th>
<th>Frequency (Morita et al.)</th>
<th>Frequency (Sykes &amp; Thorns)</th>
<th>Frequency (Thorns &amp; Sykes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (OME)</td>
<td>97</td>
<td>82</td>
<td>–</td>
<td>89</td>
</tr>
<tr>
<td>Benzodiazepines (PME)</td>
<td>94</td>
<td>27</td>
<td>82</td>
<td>–</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>36</td>
<td>43</td>
<td>35</td>
<td>–</td>
</tr>
</tbody>
</table>

OME, oral morphine equivalent; PME, parenteral midazolam equivalent; –, not applicable.

### Table 4  Comparative median doses

<table>
<thead>
<tr>
<th>Medication</th>
<th>Median dose (mg/24 h)</th>
<th>Median dose (mg/24 h) (Morita et al)11</th>
<th>Median dose (mg/24 h) (Thorns &amp; Sykes)12</th>
<th>Median dose (mg/24) (Sykes &amp; Thorns)27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (OME)</td>
<td>135</td>
<td>40</td>
<td>79.2</td>
<td>–</td>
</tr>
<tr>
<td>Benzodiazepines (PME)</td>
<td>12.5</td>
<td>10</td>
<td>–</td>
<td>23.0–52.5</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2.5</td>
<td>3.8</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

OME, oral morphine equivalent; PME, parenteral midazolam equivalent; –, not applicable.
that sedative use in this setting most likely represents ‘normal’ symptom control as opposed to ‘sedation for uncontrolled symptoms in terminally ill patients.22 It is rare in this unit that patients are deliberately sedated with the aim of unconsciousness. However, treatment of anxiety is a priority of the unit. Anxiety is a very common symptom in palliative care and there has been little written about it in this setting. One recent study found that 48% of patients had anxiety (defined as a score >7 on the Hospital Anxiety and Depression Scale – Anxiety Subscale) in a cross-sectional observation study of 178 cancer patients.34 As well as treatment of anxiety, benzodiazepines are frequently used in the treatment of delirium at the end of life.

Whilst the proportion of patients receiving haloperidol was similar to a study in Japan11 (36% vs 43%), the median dosage was slightly lower in this study (2.5 mg vs 3.8 mg per 24 h). Haloperidol is used as first line therapy for delirium. As delirium is one of the commonest indications for sedation in palliative care settings,9 it may be the reason lower benzodiazepine doses are used is because of the increased frequency of haloperidol use.

There are several limitations of this study. First, it is retrospective and data may be incomplete. Whilst the retrospective nature of the study may be a limitation, it could also be considered an advantage so that no bias in medication use was apparent. Generalization is difficult, as this was an Australian population in an inpatient palliative care setting. As well, all opioid and sedative use was titrated to patients’ symptoms and their use in other medical settings may be different. The methodology of all studies in this difficult area is open for criticism. The groups that are compared are not truly matched groups (i.e. they are not randomized nor even controlled groups). Whilst this is a limitation, it is difficult to see that in this population it will ever be possible to perform a truly matched comparison to evaluate causality. Rather, we are left with studies that look for an association between opioid/sedative use and length of survival.

The principle of double effect seems to have ‘stuck’ to the use of opioid medication in particular, and more recently, sedative medication. There is a stigma attached to these medications that they are dangerous and likely to shorten survival, but that their use is justified because of double-effect reasoning. This study adds to the weight of growing evidence from similar studies around the world that opioid and sedative medications are safe drugs and their use does not influence survival of palliative care patients. Clinicians should be confident in their safety and efficacy as long as their administration is in a similar manner to this study, that is, titrated to patients’ symptoms.

The reality of palliative care (and hopefully medicine in general) is that it is rarely necessary to use the principle of double-effect as a justification for the administration of opioids and sedatives.

ACKNOWLEDGEMENTS

The authors would like to thank all the palliative care staff who record important data, and especially Jan Burns who maintains the database.

REFERENCES

Effect of opioids and sedatives on survival

Chapter Fourteen

Survival After Enrollment in an Australian Palliative Care program

Chapter Fourteen is published as:
Introduction

In 1994 and 1996 Christakis and colleagues published articles examining how long patients lived on a hospice (community based Palliative Care in USA) program after their enrolment. (41, 42) It found that the median time was between 29 to 36 days and concluded that most patients are referred late in the course of their terminal illnesses. A similar methodology was used to analyse the time patients spent in an Australian Palliative Care program after enrolment and to also look at the time spent in Palliative Care relative to the timing of diagnosis.

This chapter was the first study to investigate the time patients spend in a Palliative care service in Australia and to assess this time in relation to the initial diagnosis. There were a number of new findings – including that this median reported time was the longest that had been reported world-wide. It also found that this longer median survival did not translate into an increase in the number of patients on a program at 6 and 12 months.
Original Article

Survival After Enrollment in an Australian Palliative Care Program

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Division of Palliative Care, Newcastle Mater Misericordiae Hospital, Waratah, New South Wales, Australia

Abstract
Palliative care services aim to achieve the best quality of life for patients by controlling pain and other physical symptoms and attending to their psychospiritual needs. There have been many studies across different countries looking at timing of referral to palliative care services. Almost universally, timing of referral to palliative care is ‘late’ in the course of the patients’ illness. This study looked at survival of patients after enrollment in an Australian integrated palliative care service that consists of inpatient beds (hospice), community care and consultation services. We analyzed the survival of 1138 patients enrolled over a 30-month period. The mean age was 70.1 years and 55% of the patients were male. The most common cancers were lung (19.1%), colorectal (13.4%) and prostate (5.8%), with nonmalignant disease accounting for 5.6% of all patients. The median length of survival was 54 days, with 9.3% of the patients dying within 7 days and 16.96% of patients living longer than six months. Perhaps more importantly than median survival is the time spent on a palliative care program in the overall context of diagnosis till death. The median percentage of time since diagnosis spent on the program was 17%. Timing of referral should be dependent on the need for intervention for physical or psychological symptoms. This can be meaningful whether the number of days till death is small or large. J Pain Symptom Manage 2004;27:310–315. @ 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Survival analysis, palliative care, human, mortality, neoplasms

Introduction
Palliative care services aim to achieve the best quality of life for their patients by controlling pain and other physical symptoms and attending to their psychospiritual needs. These services can be provided across many health care settings (general hospitals, inpatient palliative care units and hospices), as well as in people’s own homes. The timing of referral to palliative care services is reliant on the physician first determining a need for some intervention and second, trying to make an estimate of patient prognosis. Research has shown that doctors are not able to estimate accurately the prognosis of patients under their care.1–3 This means that for a referral to be initiated, there usually has to be a need for intervention. This
intervention may be in the form of attending to patients’ physical symptoms or in the form of psychological care, or may involve increased support for carers at home. The course of a patient with an incurable illness can be unpredictable and this intervention may be needed early on in a patient’s illness or late in their disease process.

There have been several studies in different countries looking at survival of patients after enrollment in palliative care programs. Most have shown a median survival of 11 to 38 days. Median survival on palliative care programs has been analyzed in isolation from the overall survival of patients from the time of diagnosis till the time of death. What is unknown from these studies is whether the patients were referred late in their illness to the palliative care service because they were diagnosed late in their disease process or whether they had no problems requiring palliative care intervention until late in their illness. Because of the short times on palliative care programs, there have been calls to move away from a traditional ‘curative approach initially followed by palliative care approach’ to what has been termed a ‘mixed management model’, where there is the administration simultaneously of disease-modifying therapies and palliative measures.

Few studies have looked at Australian palliative care services and those published have looked at inpatient settings and found a median survival of only 14 to 15 days. Palliative care in Australia is a mixture of inpatient palliative care units (hospices, hospital-based beds), community based care and consultation services.

The aims of this study were threefold: 1) to look at the survival of patients after enrollment in an Australian integrated palliative care service consisting of inpatient beds (hospice), community care and consultation services; 2) to compare the survival in this cohort to a large previous study; and 3) to determine how much time is spent on a palliative care program compared to the time from diagnosis till death.

**Methods**

The Newcastle palliative care service is a multidisciplinary service that manages both inpatients (in a twenty-bed hospice) and patients in the community. Community patients are either in their own homes or residential care facilities such as nursing homes or hostels. There is also a consultative service to all hospitals in the Hunter area. This is a health region of New South Wales, Australia that services approximately 527,000 people.

Patients were included in this study if they were admitted to the Newcastle palliative care service between January 1, 1998 and June 30, 2000. Follow-up with respect to mortality was obtained until June 30, 2001 (minimum 12 months). Data were obtained retrospectively from a computerized database at the Newcastle Mercy Hospice designed by one of the authors. All patients referred to the service had demographic and clinical data recorded in this database. During their clinical course, all members of the palliative care team recorded further clinical data.

There were 1159 patients admitted to the service during the 30-month period. Of these patients, 12 were discharged from the service as they were deemed no longer needing palliative care input, and 9 were discharged to a palliative care service outside the Newcastle area and follow-up was not obtained. This left 1138 patients on whom data were analyzed. At the end of the follow-up period, there were 21 patients still alive. This was verified via contact (telephone or in person, by a member of the service) with the patients either on or after June 30, 2001. There were two patients whose date of death was unable to be pinpointed, but the place of death was identified.

The dependent variable in this study was length of survival after enrolment in the program. The independent variables were patients’ age, sex, diagnosis (according to ICD 10 classification), referring doctor (specialist versus general practitioner), site at which patient was first seen, place of death and date of diagnosis. Diagnoses were grouped into 16 categories as shown in Table 1. Patients with missing data on date of diagnosis were excluded from that analysis.

Statistical analysis was performed using STATA 5.0 software (Stata, College Station, TX).

Ethics approval was obtained from the Hunter Area Region Ethics Committee.

**Results**

**Characteristics**

The age of the patients ranged from 1 to 102 years. The mean age (± SD) was 70.1 ± 12.8
Table 1

Diagnostic Groups

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>217</td>
<td>19.1</td>
</tr>
<tr>
<td>Colon or rectum</td>
<td>152</td>
<td>13.4</td>
</tr>
<tr>
<td>All other malignancies</td>
<td>98</td>
<td>8.6</td>
</tr>
<tr>
<td>Prostate</td>
<td>66</td>
<td>5.8</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>65</td>
<td>5.7</td>
</tr>
<tr>
<td>Breast</td>
<td>64</td>
<td>5.6</td>
</tr>
<tr>
<td>Nonmalignant</td>
<td>64</td>
<td>5.6</td>
</tr>
<tr>
<td>Leukemia or lymphoma</td>
<td>61</td>
<td>5.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>61</td>
<td>5.4</td>
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<tr>
<td>Upper GIT</td>
<td>59</td>
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<tr>
<td>Melanoma</td>
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<td>4.6</td>
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<tr>
<td>CNS</td>
<td>43</td>
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</tr>
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<td>Female genital tract</td>
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<td>3.7</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>37</td>
<td>3.3</td>
</tr>
<tr>
<td>Skin (not melanoma)</td>
<td>30</td>
<td>2.6</td>
</tr>
<tr>
<td>Liver or biliary tract</td>
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<td>2.4</td>
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</tbody>
</table>

years and 55% of the patients were male. The most common cancers were lung (19.1%), colorectal (13.4%) and prostate (5.8%). Nonmalignant disease accounted for 5.6% of all patients (Table 1). This included stroke, congestive heart failure, dementia, chronic airway limitation and other degenerative neurological conditions. The patients were referred fairly evenly between specialists (48.9%) and general practitioners (51.1%).

Survival

The median length of survival (after enrollment) was 54 days (95% CI 48 to 57) (Fig. 1).

![Fig. 1. Kaplan-Meier survival curve for 1,138 patients enrolled in palliative care service.](image)

Of the patients who died, 9.3% died within 7 days (Table 2). At the other end of the spectrum, 16.9% of patients were alive at 180 days and 6.1% of patients were alive longer than one year after referral to our service. The people who lived longer than 180 days after enrollment were more likely to have cancers of the prostate, skin, breast or central nervous system. Of the patients who died, there were 1037 patients on whom a date of diagnosis was known. In this group, the median time from diagnosis to death was 380 days (95% CI 338 to 421; range 6–10,794), and the median time of diagnosis to referral to the palliative care program was 255 days (95% CI 218 to 293; range 0–10,781). Within this group of patients, if the time spent on the palliative care service is expressed as a percentage of the time from diagnosis till death, the median value is 17% (95% CI 16 to 20) (Fig. 2). The characteristics of the patients on whom a date of diagnosis was known were compared to those for whom this data was missing. This showed no systematic variation.

Median survival was also assessed according to the site at which the patient was first seen (Table 3) and according to the referring doctor (Table 4). There was no significant difference in survival according to the different specialties of referring doctors ($P = 0.57$, log-rank test for quality of survivor functions). However, in terms of site of first contact, there was a significant difference between the hospice and both the community and hospital consults ($P < 0.005$, log-rank test for equality of survivor functions). In terms of referring specialty, referrals from general practitioners had a median survival of 50 days, whereas those from specialists had a median survival of 57 days.

Disease-Specific Survival

The proportion of patients who died within 7 days varied from 13.8% for urinary tract malignancies to 2.4% for female genital tract malignancies. In those patients who lived longer than 180 days, the proportion ranged from 5.8% for melanoma to 30.3% for prostate. The median survival was shortest for melanoma at 46 days and longest for prostate at 98 days.

Place of Death

There were 1117 deaths during the study. Of these patients, 370 (33%) died in the community (home, hostel or nursing home), 583

Fig. 1. Kaplan-Meier survival curve for 1,138 patients enrolled in palliative care service.
Table 2
Survival According to Diagnosis Among 1138 Patients Admitted to the Newcastle Area Palliative Care Service Between 1/1/1998 and 6/30/2000

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>Median Survival</th>
<th>% Dying within 7 Days</th>
<th>% Living &gt;180 Days</th>
<th>% Time Spent on Service</th>
</tr>
</thead>
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<tr>
<td>MALIGNANCIES</td>
<td></td>
<td></td>
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<tr>
<td>Melanoma</td>
<td>52</td>
<td>4.6</td>
<td>3.9</td>
<td>5.8</td>
<td>14.8</td>
</tr>
<tr>
<td>Leukemia or lymphoma</td>
<td>61</td>
<td>5.4</td>
<td>3.9</td>
<td>14.75</td>
<td>10.6</td>
</tr>
<tr>
<td>Upper GIT</td>
<td>59</td>
<td>5.2</td>
<td>8.2</td>
<td>11.9</td>
<td>19.34</td>
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<tr>
<td>Lung</td>
<td>217</td>
<td>19.1</td>
<td>8.8</td>
<td>15.67</td>
<td>16.6</td>
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<tr>
<td>Breast</td>
<td>64</td>
<td>5.6</td>
<td>8.2</td>
<td>15.67</td>
<td>14.6</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>37</td>
<td>3.3</td>
<td>2.7</td>
<td>13.51</td>
<td>26.7</td>
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<tr>
<td>Pancreas</td>
<td>61</td>
<td>5.4</td>
<td>9.8</td>
<td>11.48</td>
<td>28.9</td>
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<td>Liver or biliary tract</td>
<td>27</td>
<td>2.4</td>
<td>7.4</td>
<td>11.7</td>
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<td>Colon or rectum</td>
<td>152</td>
<td>13.4</td>
<td>8.6</td>
<td>13.82</td>
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<td>Urinary tract</td>
<td>65</td>
<td>5.7</td>
<td>13.85</td>
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<td>17.9</td>
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<tr>
<td>CNS</td>
<td>43</td>
<td>3.8</td>
<td>4.7</td>
<td>23.26</td>
<td>30.4</td>
</tr>
<tr>
<td>Female genital tract</td>
<td>42</td>
<td>3.7</td>
<td>2.4</td>
<td>19.05</td>
<td>21.2</td>
</tr>
<tr>
<td>Skin (not melanoma)</td>
<td>30</td>
<td>2.6</td>
<td>3.3</td>
<td>26.67</td>
<td>25.4</td>
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<tr>
<td>Prostate</td>
<td>66</td>
<td>5.8</td>
<td>9.1</td>
<td>30.30</td>
<td>22.4</td>
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<td>All other malignancies</td>
<td>98</td>
<td>8.6</td>
<td>8.2</td>
<td>18.37</td>
<td>15.6</td>
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<td>NONMALIGNANT DISEASE</td>
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<td>Stroke</td>
<td>3</td>
<td>0.3</td>
<td>100.00</td>
<td>—</td>
<td>1.7</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>8</td>
<td>0.7</td>
<td>50.00</td>
<td>12.50</td>
<td>9.7</td>
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<td>Dementia</td>
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<td>0.6</td>
<td>42.86</td>
<td>14.29</td>
<td>3.5</td>
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<td>Congestive heart failure</td>
<td>15</td>
<td>1.3</td>
<td>13.33</td>
<td>26.67</td>
<td>15</td>
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<tr>
<td>All other nonmalignancies</td>
<td>51</td>
<td>2.7</td>
<td>25.81</td>
<td>9.7</td>
<td>17.3</td>
</tr>
<tr>
<td>Total</td>
<td>1138</td>
<td>100</td>
<td>9.31</td>
<td>16.96</td>
<td>17.0</td>
</tr>
</tbody>
</table>

(52%) died in the inpatient beds at the hospice and 165 (15%) died in other hospital-based beds.

Discussion

This study found the overall median survival of patients admitted to this palliative care service was 54 days. This is substantially longer than any other published series of either inpatients, outpatients or a combination. As found previously, there is a large variation in survival after enrolment according to diagnosis. There seems to be two possibilities as to why our cohort had a longer median length of survival. Either they were referred earlier to the service or they lived longer on the service because of some intervention. While the second possibility has had little discussion in the medical literature, this service aims neither to prolong nor hasten death or dying, but rather aims to maximize quality of life. Therefore, it seems most likely that earlier referral is the explanation.

There are many reasons why earlier referral may occur in this service. Ease of access for referrals is provided through a central referral phone number. Patient referrals always involve a medical practitioner—and this is split almost 50:50 between general practitioners and specialists. While medical and radiation oncology specialists predominate as the major referral sources, there are many other non-oncology specialties involved in the referral of patients to this service. In this service, there is a high priority given to close contact with other health professionals, especially community
nursing and allied health professionals. The patients’ general practitioners are considered part of the palliative care team, particularly in the community where they are seen as the primary health carer at all times. The vast majority of patients had a diagnosis of cancer and there is close liaison between the oncology and palliative care services. Patients can still be on chemotherapy and have other ‘active’ treatments while on the service, hopefully allowing a smooth transition when these are no longer considered appropriate. From the outset, all patients referred are reviewed by a medical staff member of the service and then a decision is made as to whether they are appropriate for the palliative care service. Another reason that this service’s patients may have a longer survival is the low number of nonmalignant patients. While this may seem counterintuitive given the unpredictability of the prognosis of some of these patients, their overall prognosis has been short in most published studies. Finally a substantial amount of time is spent on education via formal teaching to local referrers and there is an emphasis on personal feedback, given to these referrers, about their patients.

One concern may be that with a longer survival on this program there will be more patients living past 6 or 12 months. Interestingly, compared to Christakis and Escarce, there were slightly more living at 6 months (16.9% vs. 14.9%), but there were fewer alive at 1 year (6.1% vs. 8.2%). This shows that increasing median survival time will not necessarily increase the number of patients on a program at 6 or 12 months. As well, the number of patients who die within 7 days of referral is 9.3%, which is lower than the 15.6% found in Christakis and Escarce. This may suggest that there were fewer “very late referrals” in this cohort.

This study is the first to look at referral and overall disease duration in the same group of patients. In this cohort the median percentage of time spent on a palliative care program, in relation to diagnosis to death, was 17%. To illustrate this point further, if a patient with breast cancer is diagnosed ten years before death and is referred to a palliative care service 100 days before death, the absolute value of survival on a palliative care program looks long (i.e., ‘early’ referral). In relation to their date of diagnosis, this is quite a ‘late’ referral. The opposite case to this is a patient diagnosed with pancreatic cancer and surviving thirty days from diagnosis till death. If referred to a palliative care service 15 days before death, they can be easily considered a ‘late referral’, when in fact the patient has spent 50% of their time from diagnosis till death on a palliative care program.

This study has shown that referrals to palliative care services can occur ‘early.’ We would also argue that it is more relevant to look at the time spent on a palliative care program in the overall context of the patients’ survival rather than absolute days. Importantly, because doctors are so poor at prognostication, patients should be referred when there is a need for palliative care intervention. We believe effective education of those referring to the service is the key. If intervention can make a difference to a patients’ quality of life, it is irrelevant whether it is one day or fifty days before death.

**Table 3**

<table>
<thead>
<tr>
<th>Site of First Contact</th>
<th>Patients</th>
<th>Median Survival (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient in hospice</td>
<td>149</td>
<td>13.1</td>
</tr>
<tr>
<td>Hospital</td>
<td>89</td>
<td>7.8</td>
</tr>
<tr>
<td>Community</td>
<td>900</td>
<td>79.1</td>
</tr>
<tr>
<td>Total</td>
<td>1138</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 4**

<table>
<thead>
<tr>
<th>Referring Specialty</th>
<th>Patients</th>
<th>Median Survival (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practitioner</td>
<td>581</td>
<td>51</td>
</tr>
<tr>
<td>Oncologist—Medical/Radiation</td>
<td>266</td>
<td>23</td>
</tr>
<tr>
<td>Hematology</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>115</td>
<td>10</td>
</tr>
<tr>
<td>Surgeon</td>
<td>115</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1138</td>
<td>100</td>
</tr>
</tbody>
</table>

**Acknowledgments**

The authors wish to express their sincere thanks to Dr. Kate D’Este for her help with the statistical aspects of this paper and to Dr. Simon Wein and Dr. Helen Austin for their review of the manuscript.
References


Chapter Fifteen

What are the essential medications in palliative care? - a survey of Australian palliative care doctors

Chapter Fifteen is published as:
Introduction

The best use of essential medications and the evidence for their benefit are really important aspects of pharmacology in Palliative Medicine. There had been great disparity across Australia in terms of use and availability of medications, but little in the way of documenting this, and producing a way forward. To enable this to happen a survey of Palliative Care practitioners in Australia was performed to determine what was seen as a list of essential medications and also to capture what the best quality evidence was for their use.

This study asked Australian Palliative Medicine doctors, what they thought were the essential medications in Palliative Care. This study was a driving factor for Pharmaceutical Benefits Scheme (PBS) changes in access to medications for Palliative Care patients – leading to the first ever section in the PBS for a specific patient population, as well as leading to the establishment of the Palliative Care Clinical Studies Collaborative – which is a collaboration of Australian researchers aiming to perform high quality studies to improve the evidence for medication use in Palliative Care.
What are the essential medications in palliative care?
A survey of Australian palliative care doctors

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Evidence from systematic review of all relevant randomised controlled trials</td>
</tr>
<tr>
<td>Level 2</td>
<td>Evidence from at least one properly designed randomised controlled trial</td>
</tr>
<tr>
<td>Level 3</td>
<td>Evidence from nonrandomised controlled trials, cohort studies, case control studies</td>
</tr>
<tr>
<td>Level 4</td>
<td>Evidence from case reports/expert opinion</td>
</tr>
<tr>
<td>Level 5</td>
<td>Unknown to respondent what level of evidence exists</td>
</tr>
</tbody>
</table>
current National Health and Medical Research Council (NHMRC) guidelines² 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 5–48). Most respondent’s (98%) 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>
<thead>
<tr>
<th>Palliative symptom</th>
<th>Drug</th>
<th>% of respondents nominating this drug as first rank</th>
<th>PBS subsidy at time of survey (September 2000)</th>
<th>Level of evidence nominated by respondents</th>
<th>% responding</th>
<th>Level of evidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain using opioid analgesics</td>
<td>Morphine</td>
<td>98</td>
<td>Yes</td>
<td>1</td>
<td>43</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>12</td>
<td>3</td>
<td>9</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Pain using nonopioid analgesics</td>
<td>Paracetamol</td>
<td>88</td>
<td>Yes</td>
<td>1</td>
<td>43</td>
<td>1</td>
<td>5</td>
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<td>Pain using adjuvant analgesics</td>
<td>Valproate</td>
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<td>Yes</td>
<td>1</td>
<td>8</td>
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<td>Dyspnoea</td>
<td>Morphine</td>
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<td>No</td>
<td>1</td>
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<td>5</td>
<td>31</td>
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<tr>
<td>End stage respiratory reflexes (grunting, secretions)</td>
<td>Hyoscine</td>
<td>88</td>
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<td>4</td>
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<tr>
<td></td>
<td>Hydrobromide</td>
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<tr>
<td>Terminal restlessness</td>
<td>Midazolam</td>
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<td>No</td>
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<td>Anorexia</td>
<td>Dexamethasone</td>
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<td>Nausea</td>
<td>Metoclopramide</td>
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</table>
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

<table>
<thead>
<tr>
<th>Palliative symptom</th>
<th>Drug</th>
<th>% of respondents nominating this drug as first rank</th>
<th>PBS subsidy at time of survey (September 2000)</th>
<th>Level of evidence nominated by respondents</th>
<th>% responding</th>
<th>Level of evidence</th>
<th>Reference</th>
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<td>Constipation</td>
<td>Docusate and senna</td>
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<td>No</td>
<td>1</td>
<td>9</td>
<td>4E</td>
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<td>Dry mouth</td>
<td>Artificial saliva</td>
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<td>Delirium</td>
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<td>Anxiety</td>
<td>Diazepam</td>
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<td></td>
<td>5</td>
<td>54</td>
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</table>

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 2.

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. 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.

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 3–6, while more than one in 3 respondents thought morphine only had level 4 or 6 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.
### 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 Palliative Medicine and Palliative Care Australia for support.

### References


### Table 3. Ranking of ‘essential’ drug, compared with those of a previous world survey

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Main palliative care indication</th>
<th>Rank number of a previous (world) survey</th>
<th>Highest level of evidence</th>
<th>Current PBS listing (December 2005)</th>
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<tbody>
<tr>
<td>1</td>
<td>Morphine</td>
<td>Pain</td>
<td>1, 5*</td>
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<td>Yes</td>
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<td>2</td>
<td>Haloperidol</td>
<td>Delirium</td>
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<tr>
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<td>Dexamethasone</td>
<td>Anorexia/cachexia</td>
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<td>Midazolam</td>
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<td>9</td>
<td>No</td>
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<td>Metoclopramide</td>
<td>Nausea/vomiting</td>
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<td>18</td>
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</tr>
<tr>
<td>6</td>
<td>Clonazepam</td>
<td>Terminal restlessness</td>
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<tr>
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<td>Paracetamol</td>
<td>Pain</td>
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<td>Amitryptiline</td>
<td>Neurophysic pain</td>
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<td>Hyoscyamine hydrobromide</td>
<td>Excess oropharyngeal secretions</td>
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*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.

### Table Analysis

This table ranks essential medications in palliative care, comparing them with previous world surveys. The table includes ranking numbers, main palliative care indications, and dosing information for each medication. The highest level of evidence and current PBS listing (December 2005) are also provided.
Chapter Sixteen

Conclusions
16.1 Principal findings

The principal findings of this thesis were:

1. Approximately half of interventions (48%) performed in an inpatient Palliative Care population were based on randomised controlled trials. (35)

2. There are insufficient good quality studies to make any recommendations for practice with regard to the use of medically assisted hydration or medically assisted nutrition in Palliative Care patients. (43, 44)

3. Palliative doctors and nurses believe that medically assisted nutrition and hydration at the end stage of life rarely benefit patients and as long as adequate mouth care is given, patients do not suffer. However, family members do experience emotional distress in dealing with this situation. (45)

4. There are contesting discourses for nurses and doctors when nutrition and hydration is ceased that involve maintaining quality of life versus the prolongation of life. (46)

5. In the acute hospital setting the views of doctors in regards to MAH represents a professional and personal struggle involved in attending to those who are dying. This discourse of uncertainty is associated with the transition from a curative to a palliative approach to care, consultation with patients and their families, the cultural expectations of patients and their families, the effects of dehydration and technology and the influence of media on expectations of cure over care. (47)

6. A prospective open label study found that in an inpatient Palliative Care unit, “burst” ketamine protocol was relatively safe and simple with a reasonable (50%) response rate. (48)
7. In an prospective audit a ‘burst’ triple-agent approach was safe and effective in an inpatient Palliative Care population during episodes of poorly controlled acute on chronic pain. (49)

8. Intranasal sufentanil can provide relatively rapid onset, intense, but relatively short lasting analgesia and in the Palliative Care setting it is an effective, practical, and safe option for breakthrough pain. (50)

9. Dexamethasone and midazolam should not be combined in syringe driver solutions, as their combination leads to the significant loss of midazolam. As well, the cloudiness of a solution is not the only predictor of drug loss and that drug loss may occur even in solutions that remain clear at time of preparation. (51)

10. There is significant loss of clonazepam when it is infused from syringe drivers through PVC tubing, that does not occur when solutions are infused through non-PVC tubing. (52)

11. There was no association between the doses of opioids and sedatives on the last day of life and survival (from hospice admission to death) in this population of Palliative Care patients. (53)

12. The median length of survival (after enrolment on an Australian Palliative Care program) was 54 days, with the median percentage of time since diagnosis spent on the program being 17%. (54)

13. A list of 20 essential medication in Palliative Care, as determined by Australian Palliative Care doctors, and the evidence in support of their use. (55)
16.2 Implications

The development of evidence has been rapid and ongoing in the field of Palliative Medicine. This thesis has explored the various ways of increasing the knowledge base in this field.

The initial impetus was the original study examining how much everyday Palliative Care practice was evidence based. This has led onto a number of studies that have made an original and significant contribution to the evidence base of Palliative Medicine and also led to a change in practice.

1. *Inpatient Palliative Medicine is evidence based.* (35)

This study was the first to look at how much everyday practice was based on evidence. It followed a typical approach of the time, of simply looking for evidence to support an intervention. This has evolved to a more modern approach of not only looking at trials of the relevant intervention, but also then looking at the quality of the trial and grading the evidence. (56)(37) As well as evaluating the idea of evidence-based Palliative Care (57), it helped stimulate the debate on whether there is too much “medicalisation of dying”. (15) Clark points out that almost all the interventions in this original study were for physical symptoms, with little discussion about other aspects of Palliative Care. (15) The challenge for the future will be to perform high quality studies of interventions as well as working out the best ways to improve the quality of care in the other aspects of Palliative Care, such as social and spiritual components.

2. *Medically assisted nutrition and hydration for Palliative Care patients.*

These two studies have highlighted how despite vigorous ethical and philosophical debates about the provision and non provision of medically assisted nutrition and hydration, there is still little evidence to guide practice. There have been attempts at
RCTs in this area (58), but have been limited by inadequately powered studies. Currently underway is a larger trial to study the benefits of parenteral hydration in advanced cancer patients. (59)

3. **Qualitative studies of medically assisted nutrition and hydration at the end of life.** *(45-47)*

Two of the main goals of medicine are to prolong life and relieve suffering. As a patient’s incurable illness progresses, and certainly towards the end of life, these two goals can cause some conflict with patients, carers and health practitioners. The first of these qualitative studies examining the experiences of Palliative Care doctors and nurses found that they did not think medically assisted nutrition and hydration benefited patients at the end of life. This contrasted somewhat with acute hospital doctors where there wasn’t such unanimity. It also highlighted the struggle that patients, carers and health practitioners have when withdrawing life sustaining treatments and the ‘symbolism’ of this. Whilst ethically, withdrawing and withholding treatments are often seen as equivalent in clinical practice, (60) there are often strong emotions surrounding this difficult time, that mean judgements of treatments are not always based on clear reasoning from all those involved. In fact contrary to the views of the Palliative Care professionals in these papers, a recent study has shown that to caregivers and patients, hydration is seen as “meaning hope and comfort”. (29)

4. **“Burst” ketamine in refractory cancer pain.** *(48)*

This was a prospective study that followed more patients than a previous similar study. (38) This has led onto several RCTs studying the Ketamine versus placebo for poorly controlled pain in patients with cancer. The first is a small RCT examining intravenous ketamine versus placebo. Only a small number of patients were recruited (20) and there was no difference found between the two arms. (61) A larger RCT has been...
performed by the PaCCSC group, but it only has been presented in abstract form, with preliminary results would suggesting once again that Ketamine was no more effective than placebo. (62) This is an example of where large positive results in prospective studies may not be replicated in RCTs. It is always important to look at inclusion/exclusion criteria to assess the generalisability of these studies. (63)

5. 'Triple-agent' therapy for episodes of acute on chronic pain. (49)

This multimodal approach to pain management needs to be examined in well designed RCTs to definitively determine the benefit over current “uni-modal” approaches. Currently the approach is to start off with a single analgesic, maximise dose, then sequentially add in another analgesic until pain is controlled, or adverse effects occur. (64)

Furthermore, more prospective cohort studies are needed to confirm or refute the hypothesis that good pain control early in a disease process (such as cancer), will lead to less pain as the disease progresses. Associated with this would be to examine the overall analgesic consumption during the trajectory of the illness and see if it differs between either of these approaches.

6. Intranasal sufentanil for cancer-associated breakthrough pain. (50)

This novel method of delivery added to the literature another approach to breakthrough pain. Subsequently there have been various studies on the use of buccal and intranasal fentanyl preparations. Both types of preparations have now undergone RCTs comparing these new methods to placebo +/- other opioids. (65-68) The difficulty with this preparation (intranasal sufentanil) is that neither component has a patent and so
was not pursued by a pharmaceutical sponsor. The use of sufentanil in a ‘buccal’ (intranasal, sublingual) form is mainly anecdotal and pursued by individual Palliative Care units.(69-71)

7. **Compatibility and tubing effects on syringe driver infusions.** (51, 52)

These two studies on compatibility and tubing loss had significant new findings and added to the literature around use of medications in syringe drivers. It also highlighted that a lot more work is needed to obtain high quality evidence about everyday practice in Palliative Care. There are several places to obtain data about compatibility (but what is clear from these places is that the majority of information is based on anecdotal evidence and usually by visual checks).(72, 73) The first of these two studies made it clear that visual compatibility can no longer be relied upon as a standard in assessing compatibility. The second showed that the type of tubing used (PVC versus non PVC) may have clinical significance.

8. **Effects of opioids and sedatives on survival in an Australian inpatient Palliative Care population.** (53)

This study attempted to address the almost universal medical and societal perception that opioids and sedatives hasten death in the Palliative Care setting. (74, 75) It is one of many studies that has looked at opioid and sedative use at the end of life.(76-79) None have found any association between medication use and survival. These have provided reassurance to health care practitioners that, when these medications are used in response to symptom and adjusted proportionately in accordance to symptom response, they are safe to use. It has also helped add to benchmarking data about doses used and allows individual units and practitioners to compare their practice and see if there is any marked variation and to consider why that may occur. Whilst these
types of cohort studies are not at the top of hierarchal models of evidence, it is unlikely that this question will be the subject of an RCT.

Future questions include:

1. Is there a difference between opioids in efficacy and adverse effects as metabolism changes near the end of life?
2. What is the best sedative medication to use for delirium at the end of life?

9. Survival after enrolment in an Australian Palliative Care program. (54)

This study helped to characterise referral times in an Australian setting. It has been replicated in several countries around the world. (42) It has helped shape a research agenda around timing of referral, and consideration of whether early referral to Palliative Care is beneficial. A recent important study examining early referral for NSCLC has shown a significant benefit of this. (7) This has led to an important statement by ASCO, about integration and early referral to Palliative Care services. (80) It will need replication in other services around the world and in other cancer and non cancer illnesses.

10. Essential medications in Palliative Care. (55)

This survey and findings have been pivotal in setting a research agenda for high quality collaborative research trials in Australia. Some of the medications are being studied in RCTs, (6) whilst others are undergoing N of 1 studies. (24) The PaCCSC has been successful in obtaining significant government funding to perform these high quality trials which hopefully answer some crucial medication related questions in Palliative Care practice. (6, 22, 81, 82)
16.3 Future Research

High quality RCTs have been and are currently being undertaken throughout Australia and the world (83). The use of technology has facilitated this, but most importantly collaboration has been the key. Several of these studies in this thesis have been the first step to performing RCTs to enable a more definitive answer to questions about interventions. For future RCTs to succeed in Palliative Care they need to have strong methodological planning, achievable patient numbers and probably most importantly, collaboration between many centres. There is now well established a culture of performing this high quality research in Australia with several collaborative groups (PaCCS ((6), ImPaCCT (84)).

That is not to diminish non RCTs methodologies. Well designed observational studies can often answer questions just as well as RCTs.(85, 86) The problem thus far has been that in Palliative Care research there is a dearth of high quality observational studies. (87) The performance of any trial in Palliative Care needs to involve a high quality methodology so that a relevant question can have an adequate answer.

The crux of good Palliative Medicine is the doctor – patient/carer relationship. The experience of this is unlikely to be examined with an RCT, but qualitative studies will be important to work out what particular characteristics of this interaction are beneficial or not.

There needs to be a sustained and systematic approach to syringe driver use and drug compatibility.

To actually see if this research has made a difference to patient care, targeted audits or examination of evidence based practice is needed on a regular basis.
16.4 Conclusion

The challenge (and aim) of performing research in medicine is to obtain new findings that change practice. The results of the studies in this thesis have helped to improve my own practice in the following ways:

1. Having an individualised patient approach to nutrition and hydration in palliative care patients (as opposed to having blanket policies about every/no patients receiving MANH at the end of life)
2. Using rapid onset/offset medications for breakthrough pain (such as intranasal sufentanil)
3. Dexamethasone and midazolam are not combined in syringe driver solutions.
4. Clonazepam is given via non PVC tubing to prevent adsorption.
5. When teaching ethics, attention is given to the fact there is no association between opioid use and the timing of death at the end of life.
6. Referrals to Palliative Care are encouraged based on the needs of the patient, rather than a prognosis and in the knowledge that most referrals are late in the course of an illness.
7. Participation in RCTs, and N of 1 studies in Palliative Care patients.

The studies in this thesis have made a significant contribution to the understanding, practice and implications of Palliative Care interventions and interactions. It has led to further important research in interventions via high quality studies, as well as greater understanding of practice through qualitative methodology. It has shown that daily practice can be based on evidence from the literature and also challenges that as this evidence base grows, it needs to lead to higher quality patient and carer outcomes.
Appendices
Appendix 1

Statement of Contribution of Others
Statement from co-author:

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- conception and design
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- analysis and interpretation of data
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- statistical analysis
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- review abstracts
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- write review,
- write update

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- write review,
- write update.

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  write update

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- write review
- write update

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Appendix 2

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From: Phillip Good [mailto:Phillip.Good@stvincentsbrisbane.org.au]
Sent: 24 February 2012 21:03
To: Newbury, Jonathan
Subject: Re: permission to use third party copyright material (fwd)

Jonathon,

I wanted to use the articles in entirety.
I am completing a PhD by publication, so it is to be able to include a copy of those articles as part of my PhD.

Thank you

Phillip

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> >
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Thank you.

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