Acknowledgements

This pack has been written by members of the Scottish Palliative Care Pharmacists Association (SPCPA) by updating the previous SCPPE pack ‘The pharmacist in palliative care’ revised in 2004.

We gratefully acknowledge the hard work and effort made by all who contributed to this package, whether by writing, editing or peer reviewing various sections.

The Centre for Pharmacy Postgraduate Education (CPPE) in England are also acknowledged for allowing us access and use of the ‘Patients views’ used throughout the pack.

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Special thanks are also due to:
The pharmacy staff (in particular Joe Harrison) for allowing photographs to be taken.
Photography by CFH Photography.
The relevant publishers of scientific journals for granting permission to reproduce articles.
Shandwick Design, Glasgow for their hardwork and perseverance in the design of this pack.
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About this package

Welcome to this distance learning pack, which provides an overview of the pharmacists’ role for patients who require palliative care.

The delivery of palliative care is developing beyond what has traditionally been seen as care of patients with cancer to include those with other non-malignant life-limiting conditions. This involves pharmacists in developing a wider knowledge base of the particular needs of patients where different pathologies influence symptoms experienced and medicines requirements. The Audit Scotland Review of Palliative Care Services in Scotland published in August 2008, led to the subsequent national strategy document Living and Dying Well, a national action plan for palliative and end of life care in Scotland, produced by the Scottish Government in October 2008. Consultation on a Proposed Palliative Care (Scotland) Bill is currently underway. The direction of care provision is clearly outlined for care to be based on need, to have a consistent, comprehensive, appropriate and equitable application across settings, be based on dignity and respect, inclusive of patient and carer choice offering patient centred care. Pharmacists will be an integral part of the team delivering such care.

The development of newer and alternative presentations of medicines continues to increase the scope for pharmaceutical involvement in palliative care. Information needs for patients and their carers on the safe and effective use of medicines has never been greater. Patients and their families are encouraged to exercise choice in their place of care and the impact this has on the pharmacist’s role in supporting care delivery, communication and information needs across care settings is diverse. Anticipating care and planning ahead for care needs is also a challenging part for pharmacists in service delivery in an environment where continuity of care, particularly during the out of hours period may be difficult. Increasing expectation of involvement with the multi-disciplinary team presents new challenges for service delivery. This package does not consider in detail the use of complementary medicines or nutritional approaches that patients may obtain as part of self care, however pharmacists should recognise the significance of this in the holistic management of their patients. It is therefore incumbent on pharmacists to ensure that they have a good understanding of the issues and dilemmas that arise and develop the skills to offer solutions.

Within this pack we have focused on the most common aspects of palliative care. As you work through the pack, you will learn something about incidence and impact and how, as a pharmacist, you can make a significant contribution to tackling some of the problems that these create.

This pack is aimed at any pharmacist, whether working in the community, primary care or in a hospital, interested in updating and extending their knowledge about palliative care and the symptom management and support that may be considered. You may be newly qualified, a veteran in your field, or somewhere in the middle!
Successful completion will not qualify you to become an expert in palliative care, but may confirm your interest and point you in that direction. If you do want to take your learning further, there is a Diploma/Msc in Palliative Care offered by Cardiff University www.pallium.cardiff.ac.uk or Stirling University offer courses on enhanced care practice and enhanced care practice of progressive conditions.

In addition there is a NES Core Course pack on ‘Pharmaceutical Care of People requiring Palliative Care’ which provides background knowledge on palliative care and allows the pharmacist to implement a Pharmaceutical Care Needs Assessment Tool with the use of an Aide Memoire.

You can find a lot of information about the pharmacist’s role in palliative care both within this package and from the Scottish Palliative Care Pharmacists Association (a specialist interest group for pharmacy staff), and the Palliative Care Pharmacists Network www.pcpn.org.uk

Aim

The overall aim of this pack is to help you develop your knowledge and skills in relation to pharmacy services, and in particular pharmaceutical care, in relation to patients with palliative care needs, and their carers or families.

The package is designed to equip you to deliver care that is evidence based and up-to-date, while providing you with many additional sources of useful information.

To prepare and support pharmacists, prescribing advisers and pharmacist prescribers working with patients who require palliative care.

Objectives of the pack

On completion of the palliative care distance learning pack you should be able to:

- describe the common symptoms experienced by palliative care patients
- list the underlying conditions causing each symptom
- demonstrate an understanding of treatment choices for these symptoms and the pharmaceutical care issues associated with these
- list the range of equipment for medicine delivery use in palliative care.
Format

The pack is organised into an initial chapter, introducing palliative care, eleven further sections which cover the common symptoms experienced by the palliative care patient and a final chapter on medicine delivery systems used in palliative care. Most of the sections either include CPPE ‘patients’ views, one or two review articles, reproduced from various sources or will provide an electronic link to an article on the web which will offer in-depth information on the particular subject. We have also included a booklet from the BMJ; *The ABC of Palliative Care*. You will be referred to specific sections of this but will also find all of the articles of use.

The introduction to palliative care:
- gives an overview of palliative care
- includes an activity which involves collation of a local palliative care contact list.

Chapters 2-12 include the following:
- description of the symptom which is referenced
- copies of review articles (no more than two per section)
- a summary of the review articles which highlights key points
- activities (maximum of two per section) which can take the form of:
  - a case study
  - a pharmaceutical care issue table to complete
  - general questions and include suggested answers for activities (where applicable).
- references

Throughout this pack reference is made to the Palliative Care Formulary 3rd edition (PCF3). This can be accessed from [www.palliativedrugs.com](http://www.palliativedrugs.com) Registration is required, but is easy and currently free.

Some references can be accessed using an Athens password. Please follow the instructions below, if you have not already registered for an Athens password.

How to register

You can self-register for an ATHENS account. Please go to the e-Library homepage ([www.elib.scot.nhs.uk](http://www.elib.scot.nhs.uk)) and click on the “login / register” link at the top of the page.

You can then follow the process through to apply for a NHS Education for Scotland ATHENS account. Applications made from a PC on NHS premises normally receive account details the same day, those from outside the NHS network have to be verified, and so may take up to one week. In both cases, the account will not be recognised by the e-Library until the working day following the account creation, but access to subscription resources such as electronic journals and databases should be available shortly after the account details are received.
Included in some of the sections are excerpts from ‘patient’s experiences’, reprinted with kind permission from The Centre for Pharmacy Postgraduate Education (CPPE). These may assist in setting the context of the symptoms, perceptions and highlighting what these mean on a practical level for patients and their carers.

Also included are some practice points. These are optional activities which will assist practitioners in delivering palliative care on a practical level.

**Chapter 13 - Medicine delivery systems contains**:
- a detailed, referenced summary of common medicine delivery systems used in palliative care. The relevant references for this topic are detailed at the end of the chapter
- an activity involving the collection of information on medicine delivery systems used locally which can be used as a resource later
- a second activity which involves some medicine dosage calculations used in continuous subcutaneous infusions.

**Pharmaceutical care plans**

Within the pack there are a number of pharmaceutical care tables included as an activity for you to complete. These tables prompt you to think about the actions and outcomes which relate to identified pharmaceutical care issues for the chapter. These are included not for your torture (believe it or not) but because they direct you to think systematically about each issue; how you would address it and what you expect to achieve. Whatever you decide on, your answer requires to be concise and easily understood by others. This way of looking at and documenting pharmaceutical care will help you and those working with you to provide consistent, ongoing care. It will also allow risk management and quality assurance issues to be addressed, particularly around providing those parts of pharmaceutical care which are difficult to measure. As many of us find completion of such documentation alien, we have attempted to provide some guidance.

Pharmaceutical care issues are any problems or potential problems for individual patients relating to the use of their medicines. The action we want you to document is what you would do as a pharmacist to address each pharmaceutical care issue. The outcome is what you aim to achieve for the patient as a direct result of your action and should be measurable.
**Example: A patient presents with pain. He is already prescribed analgesia.**

<table>
<thead>
<tr>
<th>Pain</th>
<th>Pharmaceutical Care Plan</th>
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<tbody>
<tr>
<td><strong>Issue</strong></td>
<td><strong>Action</strong></td>
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| Compliance with existing analgesia | Check compliance | • Determine whether a full trial of existing analgesia has been given  
• Identify problems in complying |
| Pain may have changed in nature and severity | Discuss with doctor/nurse to ensure full assessment has been carried out | • Nature and severity of pain identified and related to SIGN guideline |
| Existing analgesia not adequate | Discuss appropriate analgesia with doctor  
Ensure analgesia follows recommendations in SIGN guideline | • Appropriate analgesia is provided |
| Patient/carer knowledge of medication and aims of treatment | Provide information and educate patient/carer on medication and aims of treatment | • Patient/carer has knowledge of medication and aims of treatment |

In practice, each part of the care may not seem so distinct but this process facilitates a systematic approach which is easier to monitor and document. There are at present no guidelines on the language which should be used and as this is evolving all the time the only advice on offer is KISS (Keep It Short and Simple).

**Activities**

There are various activities detailed throughout the pack which are indicated by the following icons in the margin:
How to work through the distance learning pack

Each chapter takes approximately 1–2 hours to complete. On completion of the introductory chapter, you should then complete the two chapters dealing with pain. Thereafter, the remaining chapters can be completed in any order you wish.

On completion of all chapters, the MCQ should then be attempted and returned to the NES office as a paper copy or can be submitted electronically online at the NES Pharmacy website. You may even wish to obtain the additional references listed at the end of each chapter for further study.

Notes

Although relevant to palliative care (and other specialities) the following areas have not been covered in this distance learning pack: stoma appliances, complementary therapies, medicine administration aids, oxygen usage and the management of side-effects of radiotherapy and chemotherapy. Many of these subjects have been dealt with in other NES distance learning packs and study days.

The scope of this distance learning pack is mainly focused on palliative care of adult patients with cancer with reference where possible to other non-malignant conditions requiring palliative care. However, the general principles can be applied to other patient groups.

Feedback

We hope that you find this pack a useful background and/or update for you to provide pharmacy services in relation to patients with palliative care needs. Please help us to assess the value and effectiveness of the pack by adding any comments on the relevant section of the MCQ answer sheet at the end of the pack.

The pack should take you approximately 15 hours to work through depending on your learning style and experience.
How this pack can assist your CPD

At the beginning of each chapter the objectives describe what you should be able to do when you complete that particular chapter. This is designed to help you monitor how you are progressing through the pack and to identify any further learning needs that you may have in relation to each aspect. You should use your personal CPD record to record your learning, future learning needs and changes to practice that you have implemented as a result of your learning. If the information is not detailed in the pack there may be further resources listed or websites which should provide you with the relevant information.

Keeping up to date

The lack of randomised controlled trials in palliative care mean that the evidence base for many treatments is lacking. As a result of this, there is a variability in practice nationally. The treatments suggested in this distance learning pack are considered best practice in the palliative care field but may not be supported by clinical trials and/or a marketing authorisation.

Guidance on the use of medicines outside their marketing authorisation is available\(^1\,2\).

The Scottish Medicines Consortium (SMC) provides advice to the NHS Boards across Scotland and the Area Drug and Therapeutic Committees on the status of:

- all newly licensed medicines
- all new formulations of existing medicines
- new indications for established medicines licensed from January 2002\(^3\).

There are a number of medicines included in this pack that have not been assessed by the SMC. Local formularies will also influence choice of medicine, and in addition there is always information available which is pertinent to your local situation in relation to palliative care services – you should contact your local Palliative Care Specialist Pharmacist for local guidance.

References

2 Lothian Palliative Care Guidelines: Use of palliative care medicines outside their marketing authorisation (guidance and informative leaflet). 2009.
3 Bennie M. All you want to know about how SIGN and the SMC work. Hospital Pharmacist 2004;11:158-159

Disclaimer

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Chapter 1  Introduction to palliative care
Chapter 1
Introduction to palliative care

Palliative care
The World Health Organisation definition of Palliative Care is “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:
• provides relief from pain and other distressing symptoms
• affirms life and regards dying as a normal process
• intends neither to hasten or postpone death
• integrates the psychological and spiritual aspects of patient care
• offers a support system to help patients live as actively as possible until death
• offers a support system to help the family cope during the patients illness and in their own bereavement
• uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
• will enhance quality of life, and may also positively influence the course of illness
• is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.”

Palliative care includes the care of any patient with advanced, incurable disease. Experience in the speciality of palliative medicine lies in the care of patients with cancer and, to a lesser extent, neurological disease although many of the principles can be applied to other incurable diseases. Frameworks for implementing palliative care services such as The Gold Standards Framework and The Liverpool Care Pathway for Care of the Dying Patient were initially developed for the care of patients with cancer, and are now being further developed to support the care of patients with other incurable conditions. The challenges exist to increase access to palliative care for these patients.

Patients with advanced, incurable disease have multiple symptoms that can be controlled, at least in part, by medicines. There is evidence that best practice with regard to treatment with medicines is not always followed and, as a result, symptom control is not optimal in every patient. The complexity of medicine regimens necessary to control all the patients’ symptoms makes it difficult for patients and their carers to manage their medicines and a low level of compliance is reported. The pharmaceutical care of this group of patients can be improved.
Patients with cancer may be living much longer with the condition and issues which have previously been associated with other long term conditions may now be affecting cancer patients too. Disease trajectories for conditions requiring palliative care support vary.

The role of the pharmacist in palliative care is developing. The scope of pharmaceutical services, which should be delivered to cancer patients, has been outlined in Scottish Executive guidance. The core services to be provided by pharmacists working in both hospital and community pharmacy include clinical pharmacy, medicines procurement and medicines information. Communication with patients, carers and other healthcare providers is essential for the continuity of provision of services.

Publication of the *Control of Pain in Patients with Cancer* clinical guideline by the Scottish Intercollegiate Guidelines Network (SIGN) in 2000 has been outlined in Scottish Executive guidance. The core services to be provided by pharmacists working in both hospital and community pharmacy include clinical pharmacy, medicines procurement and medicines information. Communication with patients, carers and other healthcare providers is essential for the continuity of provision of services.

Carers of patients with non-malignant conditions were interviewed regarding the care their relatives received at the end of life. These interviews were captured for a conference run by St Margaret’s Hospice, Clydebank and are available to view at the following link [www.smh.org.uk/education-conference.php](http://www.smh.org.uk/education-conference.php).
Due to patient and carer demand, community pharmacy networks were set up in some areas to ensure continuity of care, equity of access to medicines and provision of specialist pharmaceutical advice. A Scottish Executive circular issued in 1999 earmarked funding to extend these model schemes throughout Scotland\(^\text{12}\). This development has been recognised as a core patient service within the standards for palliative care set down by the Clinical Standards Board for Scotland (CSBS)\(^\text{13}\) (now part of NHS Quality Improvement Scotland). It is also identified as a positive example of the service adapting to become more patient centred in *Our National Health; a plan for action*\(^\text{14}\) and *The Right Medicine: a strategy for pharmaceutical care in Scotland*\(^\text{15}\). Pharmaceutical services for this group of patients have evolved with the development of the pharmaceutical care model schemes steps framework\(^\text{16}\). A national overview of specialist palliative care was published in January 2004\(^\text{17}\). Changes to provision of unscheduled care, since late 2004 within primary care, have increased the challenges for ensuring continuity of care and access to medicines and pharmacists can play an integral role in service delivery. These issues have been highlighted in the recent Audit Scotland Report\(^\text{18}\) and the NHS response\(^\text{19}\) which was to launch a Scottish Action Plan “Living and Dying Well” to improve palliative and end of life care for all, irrespective of diagnosis or place of care. All NHS Boards have developed delivery plans based on these.

Complementary therapies are also being self selected by patients with life limiting conditions. Patients require access to reliable information about these therapies in a way which protects patients’ safety\(^\text{20}\). Pharmacists can signpost information as part of the provision of pharmaceutical care (also refer to NES pack on complementary therapies).

The following articles give a general overview of palliative care. In addition they cover aspects of symptom control which will give some insight into the remainder of the distance learning pack.

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**Now read** Palliative Care from the *Pharmaceutical Journal* by Urie J et al and also refer to Section 1 ‘The principles of palliative care’ and Section 5 ‘Chronic non-malignant disease’ in *The ABC of Palliative Care (second edition)* included with this pack.
PHARMACEUTICAL CARE

(10) PALLIATIVE CARE

By Jane Urrie, BSc, MRPharmS, Helen Fielding, MSc, MRPharmS, Dorothy McArthur, MSc, MRPharmS, Maira Kinnear, MSc, MRPharmS, Steve Hudson, MPharm, FRPharmS, and Marie Fallon, MD, FRCP

Palliative care is the care of any patient with advanced, incurable disease. It involves the control of symptoms, such as pain, and aims to improve quality of life for both patients and their families. This article specifically examines palliative care for cancer patients.

Palliative care aims to provide relief from suffering and improve the quality of life of both patients and their families. Palliative care takes a holistic approach which acknowledges that suffering is more than physical distress and recognises that patients require a combination of physical, psychological, social and spiritual care. A definition of palliative care is given in Panel 1.

Palliative care is the care of any patient with advanced, incurable disease. At present, co-ordinated palliative care is usually only available to patients with cancer and neurological diseases. However, there is evidence supporting the need for palliative care to be provided for patients with advanced cardiac and respiratory disease. The scope of this article is limited to palliative care for cancer patients although the general principles can be applied to other patient groups.

A large part of physical care involves symptom control, which is one of the cornerstones of palliative care. Most symptoms are controlled, at least in part, by the use of medication. Patients with cancer often have multiple symptoms, even at diagnosis. The medication regimens necessary to palliate these symptoms, and the associated pharmaceutical care, can become complex so a systematic approach is necessary. This will include recognition of the presence of symptoms, clear records of current medication, anticipation of unwanted effects of medication, and the degree of the patient’s understanding of treatment goals. Monitoring for side effects and the patient’s ability to take prescribed formulations is central to the provision of pharmaceutical care. Confirmation of adequate symptom control and the prompt review of medicine use to identify therapeutic failures are necessary to ensure treatment success. This field of care gives pharmacists many opportunities to contribute to pharmaceutical care within the multidisciplinary team.

PUBLIC HEALTH ISSUES OF PALLIATIVE CARE

One in three of the population will develop cancer during their lifetime. Of the 250,000 new cases of cancer reported in the UK in 1995, two-thirds were in people over...
Panel 1: WHO definition

**World Health Organisation definition of palliative care**

“The active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families.”

Panel 2: Profile of palliative care of cancer patients in the population of a pharmacy serving 5,000 patients

About 1,500 patients will develop cancer during their lifetime.

125 patients will have a current diagnosis of cancer.

40 patients will have a chronic disability related to this diagnosis.

Annually there are 13 deaths from cancer:

- Three from lung cancer
- One or two from colorectal cancer
- One from breast cancer
- One from prostate cancer

Of the 13 who die:

- 12 will spend the majority of their last year at home
- 11 will be admitted overnight to hospital at least once
- Four will die at home — this may be higher in rural areas (up to eight)

Annually there are:

- 21 new cases of cancer diagnosed (14 in those aged over 65 years)
- Of the 21 new cases, there are:
  - Three or four lung cancer cases
  - Three breast cancer cases
  - Two or three colorectal cancer cases
  - One or two prostate cancer cases
  - Ten other cancer types

Table 1: Prevalence of symptoms in cancer
table patient population

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>50-70</td>
</tr>
<tr>
<td>Weight loss</td>
<td>45-70</td>
</tr>
<tr>
<td>General weakness/fatigue</td>
<td>40-50</td>
</tr>
<tr>
<td>Anorexia</td>
<td>40-75</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30-60</td>
</tr>
<tr>
<td>Constipation</td>
<td>25-50</td>
</tr>
<tr>
<td>Depression</td>
<td>20-30</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>15-45</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>20-50</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
</tr>
</tbody>
</table>

65 years of age. It is predicted that as cancer is a disease predominantly of the elderly, the number of people with cancer will rise as the population ages. In 1996, there were 150,000 deaths from cancer which accounted for 25 per cent of all deaths. Although there are over 200 different forms of cancer, half of all new cases are lung (17 per cent), breast (14 per cent), colorectal (13 per cent) and prostate (8 per cent). The same four solid tumours are responsible for half of all cancer deaths: lung (23 per cent), colorectal (11 per cent), breast (9 per cent) and prostate cancer (6 per cent). Half the cancer deaths in men are because of three cancers (lung, prostate and large bowel), and 40 per cent of cancer deaths in women are from lung, breast and large bowel cancer.

The profile of the population of an average community pharmacy, which would serve 125 patients living with a diagnosis of cancer, is illustrated in Panel 2. A proportion of this group of patients will be receiving active treatment, some will have completed active treatment and approximately 10 per cent will be approaching death. Each group has symptoms that require treatment.

**Provision of palliative care**

Patients expect health care professionals to concentrate on their ongoing symptom control and not their eventual death. Terminal care is an integral part of palliative care and is given during the last few days or hours of life. However, many patients have symptoms at the point of cancer diagnosis and palliative care should be provided from then and not confined to the phase of disease progression leading to death.

Family and friends are often intimately involved in patient care, sometimes at the expense of their own health. In one study, relatives were identified as the principal carers for over 80 per cent of those needing care at home and 6 per cent of patients relied on friends and neighbours. It has been shown that poor care prior to death makes bereavement difficult and has long-term repercussions on the health of family and friends. Care for patients’ families and friends after death is an integral part of palliative care.

Over 90 per cent of patients with cancer spend most of their last year of life at home and over 90 per cent of those patients are admitted overnight to hospital at least once during this time.

Both primary and secondary care teams deliver basic palliative care to patients. Interventions such as radiotherapy, anaesthetic nerve blocks and specialist palliative care are accessed via primary and secondary care teams. Familiarity with the services that specialists provide, and how these services are accessed, is essential for the optimisation of patients’ care.

Specialist palliative care is delivered by hospital palliative care teams, specialist palliative care units within hospitals and hospices, and home care teams within primary care. These teams can either provide all the care required for a patient or supplement on-going care. The addition of specialist care to the primary and secondary care teams means that the care of each patient often involves a complex network of doctors, nurses and other health care professionals with whom patients have contact, it is important that services are not perceived to be disorganised, or seemingly only reacting to crises rather than following predetermined plans.

The respective responsibilities of each team and individual must be clear to the patient, family and carers to prevent the potential confusion that can exist about the roles of health care professionals. There is a clear need for good documentation of care, including the patient’s pharmacological care, which should be shared by the various health care workers to secure continuity of care.

Patient-held records, including records of prescribed medication, are being developed at present. Effective use of such records requires each member of the health care team to take responsibility for documenting delivery of care.

**Symptom prevalence**

The 10 most common symptoms in patients with advanced cancer have been found to be pain, fatigue, weakness, anorexia, weight loss, lack of energy, dry mouth, constipation, dyspnoea and early satiety. Pain, fatigue and anorexia were consistently among the 10 most prevalent and clinically important symptoms among patients with cancer. Along with anxiety, these common symptoms make up the most clinically important problems in the palliative care of cancer patients. The reported prevalence of symptoms in cancer patients is given in Table 1.

Patients rarely suffer only one symptom and most patients with advanced cancer are polysymptomatic. At one pain clinic, patients with cancer of 5.5 symptoms (range one to 10). In another study, the median number of symptoms experienced by patients referred to a palliative care service was six (range of one to 25). These findings have been confirmed by similar studies. As disease progresses, the number and severity of symptoms generally increase. The relatively large number of symptoms seen by specialist palliative care services probably reflects the advanced disease stage of patients when referred.
With the exception of constipation, insomnia and confusion, which tend to appear universally in cancer,\textsuperscript{17} tumour growth causes different symptoms depending on the primary cancer site.\textsuperscript{1} Dysphagia is observed comparatively more frequently in cancer of the head and neck region; dyspnoea in cancer of the respiratory system, breast and other organs within the chest cavity; and anaemia, vomiting and urinary symptoms are most commonly observed in cancers of the gastrointestinal tract or genitourinary system.\textsuperscript{17} In prostate cancer, pain, which is often severe, is the single common symptom that is prevalent.\textsuperscript{14,15}

During the last days of life, symptoms such as pain, nausea, vomiting and constipation change little in prevalence but additional symptoms may appear. In the last weeks of fever, dyspnoea, anaemia, delirium/confusion and weight loss become more prevalent.\textsuperscript{18,19} By this stage, almost no patients are symptom free and the percentage who are completely incapacitated rises from about 1 per cent to 12 per cent.\textsuperscript{18} The most frequent symptoms in the last 48 hours are anaemia, asthenia (loss of strength), dry mouth, confusion, constipation, breathlessness and pain.\textsuperscript{18,19}

**SYMPTOM CONTROL**

Effective control of symptoms is vital to reduce suffering; in one study, 72 per cent of patients had at least a moderate reduction in their activity levels caused by the presence of symptoms.\textsuperscript{1} The control of symptoms, such as anxiety, depression, pain and dyspnoea, positively affects patients’ will to live\textsuperscript{20} as well as their ability to function normally.\textsuperscript{17}

Drug treatment plays a major role in symptom control in palliative care.\textsuperscript{21,22} However, some symptoms require other treatment modalities to be used alongside drug therapy. The treatment of dyspnoea, for example, usually includes non-drug measures such as breathing control techniques.\textsuperscript{23} Pain can be difficult to control when anxiety and depression are present, and effective symptom control may require psychological problems and spiritual needs to be addressed.\textsuperscript{24}

Effective control of a particular symptom relies on its accurate assessment—the symptom’s severity, precipitating factors and underlying causes. If possible, reversible, underlying causes should be treated; for example, a patient with a chest infection which exacerbates dyspnoea should receive an appropriate antibiotic. The presence and severity of symptoms can change as a patient’s disease progresses or as treatments, such as surgery or radiotherapy, are administered.\textsuperscript{46} These changes dictate the need for regular symptom assessment. Monitoring treatment regularly and consistently is essential to ensure benefit and to avoid harm. Predictable side effects of treatment must be anticipated and may often require the use of prophylactic medication.\textsuperscript{25}

The acceptability of treatments varies from patient to patient, depending on their priorities. For instance, driving a car may be important to a patient’s quality of life and medication which affects their ability to drive safely may be unacceptable. An individual’s priorities may also change with disease progression. For instance, bone pain may eventually lead a patient with a history of osteolytic disease to accept cancer-related osteoporosis before the use of a corticosteroid anti-inflammatory drug (with concurrent gastro-protection) for the benefit of improved mobility.

**Evidence base for treatment of symptoms**

There are few randomised, controlled clinical trials of symptomatic treatments in advanced disease.\textsuperscript{26} Difficulties in recruitment, high attrition rates, problems with obtaining consent to randomisation, in data collection and timing of the outcome assessment are barriers to conducting randomised, controlled trials in palliative care.\textsuperscript{25} These factors also limit the design and interpretation of findings in the trials which are undertaken.\textsuperscript{25}

The use of placebo treatments in controlled trials for the treatment of symptoms such as pain is often unethical.\textsuperscript{27} The Scottish Intercollegiate Guidelines Network (SIGN) has published a review of evidence to support guidelines for the treatment of chronic pain in patients with cancer.\textsuperscript{27} Shared physiological pathways of non-malignant and malignant pain allow data from the Cochrane database, and a meta-analysis by McQuay and Moore,\textsuperscript{28} on the treatment of non-malignant chronic pain to be extrapolated to patients with cancer. A summary of the evidence for treatment of chronic pain is given in Table 2. No systematic reviews of the management of other symptoms have been published. In fact, there is little published evidence of what constitutes best practice for the control of most symptoms, although there is consensus throughout Europe for some symptoms.\textsuperscript{29}

\begin{table}[h]
\centering
\caption{Table 2: Evidence base for drug treatment of chronic pain in patients with cancer}
\begin{tabular}{|l|l|}
\hline
Therapeutic intervention/strategy & Summary of findings \\
\hline
\hline
WHO cancer pain relief programme\textsuperscript{2,22} & Satisfactory pain relief can be achieved in up to 88 per cent of patients. The recommendations for each step have not been individually evaluated in randomised clinical trials \\
\hline
Non-opioids: paracetamol, aspirin, NSAID\textsuperscript{25} & All are effective in mild chronic cancer pain \\
\hline
Non-opioid with weak opioid\textsuperscript{26,28} & For mild to moderate pain, a combination preparation containing maximum therapeutic doses of a weak opioid is more effective than paracetamol alone. There is no evidence that co-codamol 8/500 is superior to paracetamol alone \\
\hline
Oral morphine\textsuperscript{21,24} & Effective for severe pain. The European consensus is that it is the drug of choice for moderate to severe cancer pain \\
\hline
Morphine titration\textsuperscript{25} & Variable individual response requires the opioid dose to be titrated carefully for each patient \\
\hline
Switching from normal-release morphine to controlled-release morphine\textsuperscript{23,24} & Same total daily dose of morphine is required regardless of formulation \\
\hline
Switching from normal-release morphine to the same at the first dose of controlled-release morphine & There is no need to administer a dose of normal-release morphine at the same time as the first dose of controlled-release morphine \\
\hline
Prophylactic laxatives with strong opioids\textsuperscript{25} & A combination of stimulant and softening laxative is required \\
\hline
Antiemetics with strong opioids\textsuperscript{25} & Reduces the level of nausea and vomiting, even with high opioid doses \\
\hline
Subcutaneous dihydrocodeine\textsuperscript{37} & Effective in controlling severe pain over prolonged periods of time \\
\hline
Alternative strong opioids\textsuperscript{15-18} & Transdermal fentanyl, oral hydromorphone and oxycodone are all as effective as oral morphine but have different side effect profiles in individual patients \\
\hline
Tricyclic antidepressants and anticonvulsants\textsuperscript{28} & Effective in treating neuropathic pain, regardless of aetiology. No measurable difference in efficacy or prevalence of side effects between the two drug groups although side effect profiles are different \\
\hline
Bisphosphonates\textsuperscript{25} & Can reduce bone pain in patients with multiple myeloma and breast cancer \\
\hline
Epidural and intrathecal opioids and/or local anaesthetic drugs\textsuperscript{42} & Can achieve analgesia at very low opioid doses with fewer opioid side effects in patients with opioid responsive pain compared with opioids delivered by other routes \\
\hline
\end{tabular}
\end{table}
Table 3: Use of adjuvant analgesics to treat specific pain syndromes

<table>
<thead>
<tr>
<th>Pain syndrome</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Bone pain</td>
<td>NSAID, single fraction radiotherapy to individual lesions, bisphosphonates*4</td>
</tr>
<tr>
<td>Neuropathic pain*9</td>
<td>Anticonvulsant or tricyclic antidepressant</td>
</tr>
<tr>
<td>Liver capsule pain</td>
<td>Corticosteroid*27</td>
</tr>
<tr>
<td>Tumour compression of another structure leading to pain</td>
<td>Corticosteroid*27</td>
</tr>
</tbody>
</table>

**Pain** Pain is suffered by 50-70 per cent of patients with cancer and is the most feared symptom.*4 The WHO analgesic ladder (Figure 1) is a validated system for treating chronic cancer pain and achieves satisfactory pain relief in up to 88 per cent of patients.*5,7

Inadequate pain assessment has been shown to be a barrier to the effective management of cancer pain.*6 Pain can be described as "what the experiencing person says it is, existing wherever he says it does."*6 Patients themselves should describe their pain as part of the assessment process because there is evidence that pain scores given by carers (professional and non-professional) can vary significantly from patient scores.*7,8

It is important to recognise that 80 per cent of patients have more than one pain*6 and 20 per cent may have four or more pains. Information on the nature and severity of each pain, along with factors that precipitate and alleviate the pain, must be obtained.*8 Using the results from this assessment, the patient is started on the step of the treatment ladder that is most appropriate for the severity of their pain.

Response to primary analgesics (non-opioids and opioids) cannot be predicted by the nature of the pain,*3 although certain types of pain, such as neuropathic pain, may require titration to higher doses, evoking more severe side effects.*2 Moderate to severe pain in cancer, whatever the aetiology, usually responds at least partially to opioids.*1 Treatment with primary analgesics should be optimised for each patient. The use of adjuvant analgesics is indicated when the patient has particular pain syndromes such as bone pain*9 or neuropathic pain*8 (Table 3). This is particularly useful when primary analgesics have a limited effect.

Anticipating and controlling the side effects of analgesics is an important part of optimising therapy. Constipation, nausea, vomiting, sedation and dry mouth are classic side effects of opioids and all are observed more frequently in patients taking opioids for moderate to severe pain than in patients not taking strong opioids.*1 Where effective prophylactic treatment is given,*6 there can be a marked reduction in side effects, despite increasing doses of opioids. Patients can be reassured that sedation should decrease 24 to 48 hours after starting a strong opioid and after each increase in dose. Tolerance to nausea usually occurs within five to 10 days of starting an opioid for moderate to severe pain, and patients should have an aminoacid to take during this period if nausea is a problem. After the initiation period, antidepressants should not be necessary. All patients receiving opioids should receive prophylactic laxatives and advice on mouth care.

Toxicity can occur in patients using opioids for pain relief.*3 The signs of toxicity are manifest when the dose of opioid is too high for the individual patient and vary from subtle confusion/agitation, vivid dreams and frank hallucinations to profound sedation followed by respiratory depression. These symptoms usually occur when the dose has been increased too far or too rapidly, and may be uncovered when the patient's background pain level has been reduced, commonly by non-drug treatments such as radiotherapy or surgery. Alternatively, the drug or its active metabolites might have accumulated because of changes in clearance, commonly caused by alterations in renal function as a result of dehydration. A small number of patients are particularly sensitive to individual opioids and may exhibit the signs of toxicity even at low doses. The severity of the signs of toxicity affects the correct dose measures required, which may vary from a reduction in opioid dose*9 to the use of naloxone. Agitation and confusion respond to haloperidol.*1 Patients who are overly sensitive to the effects of one opioid may obtain a better response from an alternative opioid.*5

**Panel 3: Definition of pain**

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such."*3

Patients and health care professionals are sometimes deterred from effective opioid use by concerns about addiction (in the form of psychological dependence) and tolerance (because of a fear of loss of clinical effectiveness over time). These concerns are obstacles to effective pain relief and are unfounded.*6 While physical dependence is a general feature of the use of opioids in chronic pain, psychological dependence is highly unlikely.*6 There is evidence that physical dependence does not occur in some patients.*6 Tolerance is not a clinically significant feature of chronic cancer pain management,*7 where increases in dose are often more required as a result of a change in the clinical condition of the patient. Social and psychological well-being is integral to the achievement of satisfactory pain control. Social and psychological needs may be important factors in the 10-15 per cent of patients whose pain apparently resists conventional approaches to analgesia. These patients may be particularly distressed and their care may have to focus on relieving anxiety and anguish. Others may require chemotherapy, radiotherapy, bisphospho-
Nausea and vomiting

Nausea and vomiting are present in 15–45% of patients with advanced cancer. These symptoms are ranked by patients as highly distressing. Nausea and vomiting are more common in those under 65 years old, in women, and in patients with stomach, gynaecological or breast cancer. There are many causes of nausea and vomiting in advanced cancer. Any reversible causes, such as hypercalcaemia, raised intracranial pressure and constipation, should be treated accordingly (see Table 4) while symptom control is sought with the use of antinaemics.

Different causes of nausea and vomiting operate via different neurological pathways and neurotransmitters. Pharmacological treatment should therefore be based rationally on the likely cause and the pathways involved (Figure 2). Antinaemics may be specific to one pathway (narrow spectrum) or may have an action on many pathways (broad spectrum). Broad-spectrum antinaemics are associated with a high incidence of side effects which may make them less acceptable to patients. A combination of antinaemics may be needed to control nausea and vomiting.

Patients who are vomiting or who have severe, constant nausea require drugs for...
symptom control to be given by a non-oral route until the vomiting is controlled.\cite{85} When control is achieved, it is important to convert back to the oral route, when possible, to maintain the patient’s independence. Medication review should be undertaken to ensure that nausea is not triggered by a specific drug formulation. Patients can have problems with taste and difficulties with swallowing tablets.

**Constipation** Constipation is prevalent in advanced cancer (25 to 50 per cent of patients) because of loss of appetite and subsequent decreased food and fluid intake, periods of immobility, drug treatments and disease involvement in the gastrointestinal tract.\cite{86} Constipation can lead to nausea and vomiting, abdominal pain or discomfort, distension, confusion and disorientation.\cite{87} Chronically constipated patients may present with overflow diarrhoea, which occurs when fluid that accumulates behind a solid faecal mass seeps past it.\cite{88}

Prophylactic laxatives should be prescribed for all patients who receive medication that causes constipation, such as opioids, tricyclic antidepressants and anticholinergics. Patients prescribed an opioid for moderate to severe pain require both a stool softening and a stimulant laxative.\cite{89} Rectal treatments may be required for patients with faecal impaction.\cite{90} Hard stools require treatment with a softening agent before purgatives are given.

**Dyspnoea** Dyspnoea is an unpleasant sensation of being unable to breathe easily and causes anxiety in both patients and their carers.\cite{23} It is most common in patients with cancer of the lung but also occurs frequently in those with disease in the chest cavity, such as cancer of the breast or oesophagus.

As death approaches, the prevalence of dyspnoea rises from 20-50 per cent to 65-80 per cent of patients and the condition increases in severity. Patients often describe feelings of constant shortness of breath, exhaustion, tightness of the chest, extreme fear of suffocation or drowning, and the need to gasp or pant. Tachypnoea (rapid breathing) often accompanies dyspnoea. If panic and anxiety are present, they lead to a central increase in the rate of breathing which further increases the feeling of breathlessness and anxiety. A vicious circle is started which is then hard to break.

The level of dyspnoea experienced is not predicted by normal tests of respiratory function\cite{91} and these tests are not useful in assessing the need for treatment or ongoing monitoring. The subjective nature of dyspnoea requires assessment based on the patient’s description of their experience.

Patients often have several different underlying factors that lead to the development of dyspnoea.\cite{92} Where appropriate, treatment of any underlying cause, such as anaemia, infection or pulmonary embolus, should be undertaken and some patients may benefit from specific anticancer treatment. There is evidence that patients with no apparent lung disease can suffer breathlessness,\cite{93} probably as a result of respiratory muscle weakness because of severe cachexia.\cite{94} Therefore, the majority of patients will require symptomatic treatment based on the clinical characteristics of their breathlessness. Patients with a history of reversible airway disease, chronic obstructive pulmonary disease (COPD) or symptoms of wheeze may benefit from regular bronchodilators. In one study, 50 per cent of patients had an element of bronchospasm to their dyspnoea.\cite{95}

All patients may be given a trial of an oral steroid, either for an anti-inflammatory effect or to reduce peri-tumour oedema, unless a contraindication exists. If tachypnoea is a major feature and respiratory difficulties, opioids are useful to decrease central respiratory drive. Smaller doses and dose increments of opioids than those used for pain relief are titrated against subjective response. Benzodiazepines are effective in low doses, particularly for patients whose anxiety augments the dyspnoea, albeit benefit in patients with no apparent anxiety can also occur, probably because of sedation and muscle relaxation. Lorazepam 0.5-2mg given sublingually can be useful in acute attacks. If regular treatment is required, diazepam 5mg daily is started and the dose slowly titrated upwards to obtain the maximum response with minimum sedation.\cite{93}

In a small number of patients, a 24-hour trial of continuous or intermittent oxygen (up to 28 per cent) may improve symptoms. Oxygen has been shown to be effective in reducing dyspnoea in patients who are hypoxic and dyspnoeic at rest.\cite{93} The therapeutic value of oxygen therapy in other groups of patients with dyspnoea is unclear.\cite{23} The use of masks can lead to difficulties in talking and eating. The apparatus itself, and the noise involved, may distance relatives. Patients often become dependent on oxygen which limits their mobility and complicates home care. For these reasons it is important only to give oxygen therapy if a clear benefit is demonstrated by careful evaluation of the 24-hour trial.

Optimal control of dyspnoea is achieved when drug treatment is given in conjunction with physiotherapy, counselling and the provision of practical aids for daily living.\cite{23}

**Last days of life (terminal care)** Up to one-third of patients are conscious until they die while another third are unconscious for longer than 24 hours before death.\cite{23} In the
last days of life, patients may become weaker and their level of consciousness may fall. Potential problems should be anticipated and response to changes must be rapid to ensure the patient’s comfort is maintained. Treatment decisions should be based on clinical findings rather than painful or uncomfortable investigations. Communication, reassurance and support of the family are essential.

During this period of change it is important for the goals of treatment to be redefined. The need for drug treatments, and the routes by which drugs are administered, require regular review. Drugs such as anti-hypertensives, antidepressants, hypoglycaemics, insulin, multivitamins and diuretics should be reviewed and may be reduced or stopped when best for the patient.

Dry mouth, confusion, dysphagia, paralysis and agitation become more common in the last week of life. If treatment for symptoms is withdrawn, the subsequent loss of symptom control can lead to further agitation in a semi-conscious or unconscious patient. Drug withdrawal syndromes associated with antidepressants and benzodiazepines can add to this agitation.

Confusion and agitation may also be caused by opioid toxicity, pain, dyspnoea, pressure sores, distended bladder or constipation and may be brought on by anxiety, anguish, loneliness and the need for reassurance. Sedation with short-acting benzodiazepines may help relieve agitation where it is not possible to treat the underlying cause without major intervention. Confusion is best treated with a neuroleptic such as haloperidol. Confused and agitated patients may require a sedating neuroleptic such as levomepromazine (meprotrimazine) or a combination of haloperidol with a benzodiazepine.

The unnecessary introduction of artificial feeding (such as nasogastric [NG] feeding), or intravenous fluids or nutrition should be avoided as the patient deteriorates. Artificial feeding has no impact on survival or patient comfort and is not appropriate in patients close to death. Inserting an NG tube or intra venous cannula causes some discomfort and such administration equipment is an unnecessary barrier between a patient and their family or carers.

A review of the literature gives conflicting reports of the physical discomfort that may be attributed to dehydration in dying patients and it remains unproven whether parenteral fluids offer symptomatic relief in this situation. Specialists agree that the priority is to prevent the symptoms associated with dehydration, rather than trying to achieve homeostasis. Hyperthermolysis, the subcutaneous infusion of fluids, is a safe and effective technique for treating dehydration. It is less invasive than intravenous therapy, technically easier to carry out and, in palliation, is used in preference to intravenous administration.

**INDIVIDUALISED CARE**

The aim of drug therapy is to control symptoms in order that quality of life can be improved. The drug regimen should not become an unbearable burden for patients and carers or provoke unacceptable side effects. As patients are often polypharmaceutical and require several drugs to control all their symptoms, the balance of benefit and detriment can be difficult to achieve as the resulting polypharmacy increases the risks of side effects, drug interactions and non-compliance. To obtain the correct balance the pharmacist can become involved in a number of key activities (see Table 5).

As the patient’s condition is labile and the response to drug therapy is variable, particularly in pain control, treatment must be tailored to their individual response to therapy. Successful drug therapy in palliative care is dependent on accurate, repeated assessment of the patient’s condition. This allows systematic choice of therapy and enables the response to treatments to be correctly assessed. Pharmacists need to liaise with other members of the care team to ensure that symptom assessment is carried out at appropriate intervals. A patient-held symptom checklist, linked to a simple severity scoring system, such as the Edmonton Symptom Assessment System, can be useful in measuring the effectiveness of interventions as well as in identifying interventions required. This particular tool has been validated in both inpatient and outpatient populations. The use of such tools might also bring to light unreported symptoms, as patients have been shown to volunteer only their most pressing problems. Care must be taken to elicit information directly from patients because assessments given by carers, including close family, do not always accurately reflect those given by patients.

While carers can identify the presence of physical symptoms, they do not accurately report the severity or level of distress caused by these symptoms. Carers also tend to overestimate the anxiety or depression suffered by patients. It is important for community pharmacists to share information on symptom assessment and response to treatment with other members of the care team.

The integration of pharmaceutical care into palliative care requires good documentation of care and a system to share this information effectively among the health care team(s). Sharing of information on the patient’s response to medication can help to maintain optimised drug treatment. Improvements in symptoms that indicate a successful response to treatment and the

**Normal meals should be retained for the social benefits of eating and should not be replaced with enteral or parenteral nutrition unless a patient cannot swallow**
identification of therapeutic failures should be recorded as part of the patient’s drug history. This information should prevent repeated trials of drugs that have previously failed to give the desired effect or have led to unacceptable side effects. Panel 4 summarises a data set for palliative care patients that might be included in a pharmacy transfer record between any care settings.

Up to 60% of patients are reported to be non-compliant with their medication regimen. Factors that make patients more likely to be non-compliant should be identified. In palliative care, the most commonly occurring risk factors are presence or fear of side effects, lack of monitoring, inadequate adjustment of therapy, practical difficulties in taking medication, old age, depression and lack of understanding of the disease and treatments. Patients with one or more risk factors require help to improve concordance and compliance.

Where the presence or fear of side effects is an issue, this can be addressed in a number of ways. Many of the side effects of drugs used for palliation of symptoms can be anticipated and managed prophylactically. Side effects can also be minimised by avoiding the use of drugs with overlapping side effect profiles. For example, the use of a tricyclic antidepressant with an antiemetic such as cyclizine can lead to intolerable anti-cholinergic side effects. Medication regimens should be reviewed regularly to identify such problems. It is important that patients and carers are educated on the common side effects to avoid any misunderstandings or confusion surrounding occurrence of unwanted effects. Because of the high number of patients who develop nausea, vomiting or dysphagia, advice is often needed on how to deliver the required drug regimen by alternative routes. For such patients the necessary drugs and equipment are often required immediately in response to rapid changes in the patient’s condition. Arrangements must be in place in each health authority to ensure that these demands can be met and that pharmacists are fully aware of such provisions.

There are particular risks associated with the use of Graseby MS26 and MS16A portable infusion devices that are used to deliver subcutaneous infusions. The risks associated with mixing a number of drugs in a small volume can be minimised by providing specialist advice on isotonicity and stability of medicines. Many of the drugs delivered in this manner are unlicensed for subcutaneous infusion. The frequent use of unlicensed medicines and the unlicensed use of existing medicines in palliative care provide several care issues for the pharmacist in terms of product availability, advice on use, formulation and monitoring. Ignorance and fear about symptomatic drug treatment is common in advanced cancer patients. One-third of palliative care patients managing their own medicines are in some way unclear about the purpose of their medication or its correct use, and a small number will not take their medication because they have no instructions on how to do so. Administration of medicines is seen as a main task of caring for the patient by 78% of carers, yet as many as 90% of carers may not be given any written information about the illness and its treatment. There is a clear need for patient and carer education about the role and use of drug treatments.

People are more likely to follow a pharmacist’s advice if they are satisfied with it. This can be achieved by adopting the right manner, dedicating an appropriate amount of time, avoiding the exclusive use of closed questions (ie, yes/no answers) and allowing the patient and carer to ask questions. Failure to remember or understand what they have been told is common and advice needs to be reinforced. Carers have identified the value of repeating information and they look for reassurance and reiteration of advice given previously. Retention of information is improved by providing information in several different formats. When providing education, it is important to know what has been said to the recipient by other members of the care team so that confusion or doubts are not introduced. Good liaison with the team is therefore necessary. Many specialist palliative care units i-
Case 1: Patient MM, female, 72 years

**Presenting symptoms**
- Low back pain and anterior chest pain leading to immobility
- Occasional nausea and vomiting

**Past medical history**
- Cancer of the breast (two years ago)
- Lumpectomy and radiotherapy
- Multiple bone metastases
- Total hip replacement
- Swollen ankles
- Dyspepsia
- Sodium 134 mmol/L, potassium 3.3 mmol/L, creatinine 100 µmol/L, urea 6.3 mmol/L, estimated creatinine clearance 49 ml/min, corrected calcium 3.46 mmol/L (corrected for low albumin)

**Current drug treatment**
- Morphine sulphate modified-release tablets 60 mg twice a day
- Morphine sulphate normal-release tablets 20 mg as required
- Diclofenac 50 mg twice a day
- Cyclizine 50 mg twice a day
- Lactulose 10 ml at night
- Bendroflumethiazide 2.5 mg daily

**PHARMACEUTICAL CARE PLAN**

<table>
<thead>
<tr>
<th>CARE ISSUES</th>
<th>ACTION TAKEN AND FUTURE PLANS</th>
</tr>
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<tbody>
<tr>
<td>1. Verify nature and extent of uncontrolled pain</td>
<td>Ascertain beliefs about opioids and identify any deliberate non-compliance linked to this. Provide education to allay fears around addiction or tolerance. Refer for full pain assessment and advise on analgesic titration. Advise patient to switch to a four-hourly regimen of normal-release morphine to determine patient's opioid requirements. Each dose one sixth of the total daily dose with extra doses of the same size given for breakthrough pain. Patients with bone metastases are likely to have bone pain — advise an increase in the dose of NSAID to maximum</td>
</tr>
<tr>
<td>2. Monitor response to analgesics</td>
<td>Liaise with medical and nursing staff to assess response to treatment on a daily basis. Monitor the use of breakthrough analgesics and ascertain their effectiveness. Ensure that opioid dose is adjusted accordingly daily. Monitor for signs of opioid toxicity. Advise that a long-acting preparation should be prescribed when dose is stabilised</td>
</tr>
<tr>
<td>3. Prompt review of management of morphine-induced constipation</td>
<td>Advise that a stimulant laxative, such as sena or bisacodyl, is required in addition to lactulose</td>
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<tr>
<td>4. Verify patient comprehension of measures to alleviate opioid-induced side effects</td>
<td>Check patient and carer are aware of common side effects of opioids and measures to prevent them. Educate on treatment of side effects, good regular oral hygiene and simple measures to avoid dry mouth. Advise patient that sedation is short-lived after each dose increase</td>
</tr>
<tr>
<td>5. Monitor GI side effects caused by NSAID</td>
<td>Discuss with medical staff. If the use of a gastroprotective agent, e.g., misoprostol 200 mg twice a day or omeprazole 20 mg daily, will prevent the development of serious GI damage in the majority of patients with existing GI damage. Advise to discontinue NSAID if dyspepsia does not improve and resolve</td>
</tr>
<tr>
<td>6. Prompt review of hypercalcaemia</td>
<td>Most patients require intravenous hydration and bisphosphonates and response to treatment should be monitored after five to seven days. Patients can develop recurrent hypercalcaemia and require monitoring every three to four weeks. Review use of thiazide diuretic</td>
</tr>
<tr>
<td>7. Prompt review of anitmetic therapy</td>
<td>Discuss with medical staff. Advise changing to antiepileptic or anticonvulsant therapy if nausea or vomiting is controlled</td>
</tr>
<tr>
<td>8. Verify patient is able to tolerate oral therapy</td>
<td>Advise on alternative routes of administration for all drug therapy until nausea and vomiting is controlled. Therapy should be changed back to oral route when nausea/ vomiting is controlled</td>
</tr>
<tr>
<td>9. Verify patient and carer understanding of drug therapy</td>
<td>Educate the patient and carer with regard to their drug therapy, particularly any changes made. Provide information on drug regimen</td>
</tr>
<tr>
<td>10. Prompt seamless provision of correct drug therapy</td>
<td>Communicate patient's ongoing care between pharmacists in each care setting. Essential for patients on complex or unusual drug regimens</td>
</tr>
</tbody>
</table>
# Case 2: Patient DL, male, 88 years

**Presenting symptoms**
- Pain in upper abdomen and left upper quadrant
- Dysphagia leading to problems with swallowing tablets
- Gastric delay causing regurgitation
- Lives alone and compliance is thought to be poor

**Past medical history**
- Persistent dysphagia
- Marked weight loss and lack of appetite
- Oesophageal adenocarcinoma (one year)
- Oesophageal dilation

**Current drug treatment**
- Morphin sulphate modified-release tablets 90mg twice a day
- Morphin sulphate normal-release solution 20mg as required
- Dexamethasone 4mg daily
- Co-danthramer liquid 10ml at night

**Patients are often more compliant with a simplified medication regimen. Therefore review to simplify and reduce risk of poor compliance**

**Stage 1**

- Normal-release morphine is given to patients receiving regular morphine to treat breakthrough pain. Dose equivalent to one-sixth of the total modified-release dose

- **Up to 60 per cent of palliative care patients are non-compliant. This is usually because of side effects or inadequate symptom control**

- **Low-dose steroids are often used to treat anorexia and cachexia. If a response is achieved treatment should be continued for three to four weeks, after this the clinical effect diminishes**

- **When switching to subcutaneous diamorphine, the conversion of oral morphine dose to the correct diamorphine subcutaneous dose must be checked**

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<td>1. Monitor patient’s ability to swallow oral medication</td>
<td>If patient is having swallowing difficulties as suspected, discuss options with prescriber. Alternatives for opioid analgesia are transdermal fentanyl patches or subcutaneous diamorphine infusion. Slow onset of action of the patch and time taken to reach full effect at each change of dose makes it inappropriate for patients with uncontrolled pain. Therefore advise on diamorphine subcutaneous equivalent dose and the need for a bolus subcutaneous diamorphine or oral morphine sulphate solution to be prescribed for breakthrough pain. Dexamethasone can be given as a once daily subcutaneous injection. The use of oral laxatives will avoid constipation</td>
</tr>
<tr>
<td>2. Prompt review of pain control</td>
<td>Refer and discuss with GP to ensure full pain assessment. Identify nature and extent of pain. Diamorphine infusion dose will require adjustment each day, based on use of breakthrough analgesics. When pain is controlled, transfer to equivalent dose of fentanyl transdermal patch</td>
</tr>
<tr>
<td>3. Monitor dosage of breakthrough analgesia</td>
<td>Discuss with GP. Breakthrough analgesia should be one-sixth of total daily dose of diamorphine/morphine. Morphine sulphate oral solution dose should initially be 30mg</td>
</tr>
<tr>
<td>4. Verify continuing need for dexamethasone</td>
<td>For cachexia/anorexia, steroids are often only effective for three to four weeks. Discuss with GP patient’s response to steroid. If no response now, consider reducing dose gradually then stopping</td>
</tr>
<tr>
<td>5. Prompt treatment for regurgitation</td>
<td>Contributing factor to loss of appetite and weight loss. Suggest addition of protonic agent such as metoclopramide, delivered by subcutaneous infusion via the syringe driver initially then orally when symptoms improve. Monitor carefully for extrapyramidal side effects as patient is at high risk because of age</td>
</tr>
<tr>
<td>6. Verify patient comprehension and monitor compliance</td>
<td>Ensure patient understanding of aims of treatment and provide education to promote compliance. Follow up during next supply of medicines. Liaise with district nurses who may be willing to attend every three days to change fentanyl transdermal patch</td>
</tr>
</tbody>
</table>
sue local treatment guidelines for symptom control. The detail in these vary because of a dearth of good evidence from randomised controlled trials. Instead, guidelines are often based on local clinical experience. Implementation and dissemination of these provide a standard level of care for palliative care patients. Clinical audit of the effect of local protocols on symptom control is essential to ensure that prescribing is effective and to allow improvements in practice. Most published literature on the involvement of pharmacists in palliative care has been descriptive. In the one published study where the impact of a pharmacist was assessed, 13 per cent of patients’ care was either improved clinically or made more cost-effective by pharmacist intervention.67 There is a clear opportunity for practice research to build in this area. Palliative care patients, particularly those at home, present many pharmaceutical care issues. Ongoing monitoring and continuity of pharmaceutical care are core issues because of disease progression and because patients move regularly between care settings. Patients and carers require more knowledge and practical support to manage their medicines effectively. Pharmacists can contribute to each of these aspects of palliative care.

REFERENCES


October 21, 2000  THE PHARMACUTICAL JOURNAL (VOL 265) 613


72. Ethical decision making. Artificial hydration (AIH) for people who are terminally ill. Eur J Palliative Care 1997;4:124.


Activity 1
Produce a list of palliative care contacts in your Health Board, which could be used as a reference source for you and your colleagues in the future. You may wish to include the following information:

- hospices (including the pharmacy supplying the hospice)
- hospital palliative care teams
- home care/Macmillan teams
- hospice/palliative care pharmacists
- community pharmacy palliative care networks
- local community dietician
- speech and language therapist
- Clinical nurse specialists e.g. MS, Parkinson’s Disease, Heart Failure, Renal Failure etc.
<table>
<thead>
<tr>
<th>Palliative Care Contact</th>
<th>Address and Contact Details</th>
<th>Role/Service Provided</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
References

Chapter 2 Pain control
Objectives

On completion of this chapter you should be able to:

- list factors which influence a patient’s perception of pain
- explain the need for regular assessment of pain
- outline the pharmaceutical care issues relevant to the management of patients with pain, using the principles of the WHO analgesic ladder
- outline the management of common side-effects induced by strong opioids.
Chapter 2
Pain control

Description of symptom
Pain is what the patient says hurts.

Pain is an individual experience. It has been clearly shown that healthcare professionals underestimate the severity of a patient’s pain whilst family and friends overestimate the suffering involved. For this reason assessment must centre where possible, with the patient’s description of the pain. Pain usually arises as a result of damage to tissues (visceral or somatic pain), but can also be caused by either damage to, or interference in, the normal functioning of neurones (neuropathic pain).

The following table lists pharmaceutical care issues relating to pain control.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Pharmaceutical Care Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Issue</strong></td>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>Presence of uncontrolled pain</td>
<td>Arrange for pain to be assessed, advise on prescription of appropriate analgesia</td>
</tr>
<tr>
<td></td>
<td>Educate patient</td>
</tr>
<tr>
<td></td>
<td>Continue to monitor pain and response to therapy</td>
</tr>
<tr>
<td>Pain perception influenced by psychological, social or spiritual issues</td>
<td>Ensure assessment addresses these aspects</td>
</tr>
<tr>
<td>Underlying cause of pain not treated</td>
<td>Discuss need for treatment with medical staff</td>
</tr>
<tr>
<td>Potential for change in nature or severity of pain</td>
<td>Ensure regular pain assessment is carried out</td>
</tr>
<tr>
<td></td>
<td>Advise on dose adjustment/ change of analgesics when indicated</td>
</tr>
<tr>
<td>Pain difficult to control</td>
<td>Seek specialist palliative care advice</td>
</tr>
<tr>
<td>Patient unable to take solid dose oral analgesia</td>
<td>Advise on alternative oral formulations, routes of administration or analgesics</td>
</tr>
<tr>
<td></td>
<td>Check dose conversions are correct</td>
</tr>
<tr>
<td>Issue</td>
<td>Action</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Potential for patient to experience breakthrough pain</td>
<td>Ensure appropriate analgesic dose is prescribed and educate patient/ carer to use correctly</td>
</tr>
<tr>
<td></td>
<td>Monitor use and efficacy of breakthrough analgesia</td>
</tr>
<tr>
<td>Regular assessment and review of pain(s)</td>
<td>Ensure assessment has been done</td>
</tr>
<tr>
<td>Regular review of patient for response to first line opioid (morphine)</td>
<td>Ensure pain is opioid responsive: determine if breakthrough doses help?</td>
</tr>
<tr>
<td></td>
<td>Ask patient, discuss with doctor and or nurse</td>
</tr>
<tr>
<td>Opioid induced constipation</td>
<td>Advise that regular laxatives are prescribed and dose adjusted as necessary</td>
</tr>
<tr>
<td>Nausea and/or vomiting following opioid initiation</td>
<td>Advise that anti-emetic prescribed, to be used if required, for up to 2 weeks after opioid started and, if needed when dose is increased</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Other opioid side-effects – dry mouth, sedation</td>
<td>Explain to patient/carer measures to manage both</td>
</tr>
<tr>
<td>Gastro-intestinal side-effects from NSAIDs</td>
<td>Assess risk and advise on prophylactic gastroprotection</td>
</tr>
</tbody>
</table>
The Patient’s View: Vicky

Vicky was diagnosed with breast cancer some years ago. These are her experiences of dealing with her pain.

“At first I thought I’d just strained myself – after all, I had moved the washing machine the previous evening. The middle of my back hurt, and so did an area below my ribs. It was not too troublesome during the day but nights were difficult as I tried to find a way to lie on my back or my front which did not hurt. I took Nurofen, then Nurofen Extra, and then added paracetamol, but nothing seemed to have much effect. I seemed to be permanently attached to a wheat bag (sometimes two).”

“After two or three weeks I went to see the doctor. He prescribed Voltarol and referred me to the hepatology department of the local hospital. My liver scan was clear and I was discharged. The Voltarol helped a bit, but it still hurt. By now I was sleeping propped up on the sofa, which seemed to be the most comfortable position for the night. I woke often and found it took about an hour of effort to relieve my back by consciously trying to relax before I could sleep again.”

“I went to back to the doctor (a different one) who suggested slow release tramadol, two a day, but both had to be taken at night to help me sleep. This gave me about 40 minutes of relief, but then the pain came back. I became very tired and could work at my editing job only when lying on the sofa. It was impossible to sit at a desk.”

“I again visited the doctor (another one) who prescribed Meptid, to be taken every three hours. He referred me to the oncology department because of my history of breast cancer seven years earlier. My CT, bone and liver scans were all clear and I was discharged – to my great relief. But the pain was still there. After a night of terrible muscle spasms the emergency doctor prescribed diazepam (5 mg). This helped. Faced with the thought of chronic pain and wondering how to deal with it, I asked my GP to refer me to the hospital rheumatology department (Voltarol and the other anti-inflammatories – which had been prescribed in sequence as one after another was withdrawn from the market because of their contribution to heart attacks – had not given me much relief). It was now, July, four months after the onset of the pain.”

Now read Section 2 ‘The principles of control of cancer pain’ in The ABC of Palliative Care (second edition) included with this pack.

Please read the following sections in the SIGN guideline No. 106 Control of pain in adults with cancer

p10-13 Assessment of pain (section 4.1-4.4)
p14-17 Principles of pain management (section 5.1-5.3)
p25-35 Treatment with Opioid Drugs (sections 7.1-7.3)
Summary of article - Control of Pain in Adults with Cancer

- The prevalence of pain in patients with cancer is around 80% (range 52-82%).
- Pain is a complex experience influenced by factors such as psychological, spiritual and social state.
- Successful pain management depends on continuing accurate assessment of pain, including the response to treatment.
- Use of the WHO guidelines, “by the mouth, by the clock, by the ladder”, will result in satisfactory pain relief in up to 88% of patients.
- The step of treatment chosen initially should be based upon the severity of the pain.
- Adjuvant analgesics and other therapies can be considered for specific pain syndromes.
- Predictable side-effects of analgesics should be prevented or minimised; for example, regular laxatives should be given to avoid constipation, and anti-emetics given for nausea and vomiting following initiation of an opioid.
- Consideration must be given to treating the underlying cause of the pain, e.g. by surgery or radiotherapy.
- Involvement of patients in their treatment has been shown to improve pain control; information and explanation about their medication should be a part of this.
- The range of opioid formulations may lead to confusion for patients between maintenance analgesia and breakthrough analgesia.
- Conversion between opioids needs careful consideration.

Practice Points

- Identify some patients who have been prescribed strong opioids for cancer pain. Review their medication records to reflect how it compares to the WHO analgesic ladder and establish if it is in line with local guidelines. Check that all patients have been prescribed laxatives. Prescribing of strong opioids by brand name is recommended for patient safety. Is this the case in your area?
- What myths about morphine have you come across patients mentioning?
- What information should be included in a leaflet for patients on opioids and driving? (If you have such a leaflet, compare it to the list above – would you add anything to it?). If you don’t have any local leaflets look at the patient information leaflets at www.palliativecareguidelines.scot.nhs.uk
- The ABCD rule:
  - Anti-emetic when starting or increasing opioids
  - Breakthrough pain – use immediate release opioid
  - Constipation (ensure softener/stimulant laxatives are prescribed)
  - Diamorphine dose in the syringe pump is one-third of the total of the regular oral morphine dose, plus the breakthrough oral morphine dose required in 24 hours
Activity 1
Work out the equivalent doses for the following:

1. Patient A has had eight 10mg doses of morphine sulphate immediate release tablets in the last 24 hours during titration of opioid requirements.

   Suggest a suitable dose of:
   (a) a modified release morphine sulphate preparation (to be given once daily)

   (b) morphine sulphate immediate release tablets to be prescribed for breakthrough pain.

2. Patient B has been receiving 60mg diamorphine over 24 hours by subcutaneous infusion. She is now able to take oral medication again, and wishes to go back to taking morphine sulphate modified release tablets (to be given twice daily). What dose would you suggest?

3. Patient C who is 61, has been taking eight co-codamol 30/500mg tablets daily, but is no longer pain free. She is not keen to have a morphine sulphate immediate release preparation every four hours as she is still working. What dose of morphine sulphate modified release tablets (to be given twice daily) would be suitable?

4. Patient D, who has severe psychiatric problems and for whom a syringe driver is considered unsuitable, cannot take his morphine sulphate immediate release solution 15mg four hourly because of vomiting. It is decided to try a fentanyl patch. What dose would you advise?

   Brand name prescribing and dispensing of modified release opioid preparations is recommended for patient safety.
Activity 2
Answer the following questions:

Mrs A is a 54 year old lady who has severe pain as a result of her ovarian cancer. From her patient medication records you see she is currently taking:
- Ibuprofen 400mg three times daily
- Paracetamol 1g four times daily
Despite taking her medication regularly, her analgesics are not providing effective pain relief and her quality of life is deteriorating as a result.

1. What recommendation would you make on Mrs A’s medication in relation to:
   - Choice and dose of analgesic
   - Any side-effects the patient may experience?

Mrs A was commenced on dihydrocodeine 30mg, four times daily, in addition to her previous analgesics. After several weeks, Mrs A presents at your pharmacy complaining of severe pain that is unrelied with her current medication.

After referring her to the GP she presents with a prescription for co-codamol 30/500mg.

2. Consider the following questions.
   - Comment on the choice of analgesic.
   - What choice and dosage of analgesic would you recommend to the GP in this situation?
   - How would Mrs A’s analgesic requirements be determined and what changes are required when this has been done?
After a few months, Mrs A seeks your advice regarding loss of pain control and severe nausea and vomiting. She is being sick at least twice daily and is worried that her painkillers are not being absorbed. Her current analgesic medication consists of:

- Morphine sulphate modified release tablets 30mg twice daily
- Ibuprofen 600mg three times daily
- Paracetamol 1g four times daily

3. What recommendations would you make on Mrs A’s medication in relation to:
   - Alternative medicines, in view of Mrs A’s nausea and vomiting
   - A suitable breakthrough analgesia?
Suggested answers

Activity 1

Work out the equivalent doses for the following:

1. Patient A has had eight 10mg doses of morphine sulphate immediate release tablets in the last 24 hours during titration of opioid requirements. Suggest a suitable dose of
   (a) a modified release morphine sulphate preparation (to be given once daily), and
   (b) the dose of morphine sulphate immediate release tablets to be prescribed for breakthrough pain.

   Morphine sulphate modified release capsules 90mg once daily; 15mg morphine sulphate immediate release tablets for breakthrough pain.

   10mg x 8 = 80mg morphine over 24 hours.
   Closest morphine sulphate modified release capsule is 90mg.
   Breakthrough dose is one sixth of the 24 hour dose = 15mg (one and a half 10mg morphine sulphate immediate release tablets).

2. Patient B has been receiving 60mg diamorphine over 24 hours by subcutaneous infusion. She is now able to take oral medication again, and wishes to go back to taking morphine sulphate modified release tablets (to be given twice daily). What dose would you suggest?

   Morphine 3mg oral = diamorphine 1mg subcutaneous.
   Morphine dose over 24 hours = 60mg x 3 = 180mg.
   Morphine sulphate modified release tablet (MST®) or capsule (Zomorph®) 90mg 12 hourly, alternatively morphine sulphate modified release tablets (MST®) or capsule (Zomorph®) 100mg twice daily means only one tablet to take per dose or
   Morphine sulphate modified release capsules (MXL®) capsules 200mg once daily.
3. Patient C who is 61, has been taking eight co-codamol 30/500mg tablets daily, but is no longer pain free. She is not keen to have a morphine sulphate immediate release preparation every four hours as she is still working. What dose of morphine sulphate modified release tablets (to be given twice daily) would be suitable?

Patient C has been taking co-codamol for some time and it may be worth exploring issues such as compliance/concordance. 7% of caucasians cannot metabolise codeine to morphine and therefore it may not be an effective choice of step 2 analgesic in this subsection of the population. Explore beliefs about changing onto a step 3 analgesic and dispel any myths about morphine.

Morphine sulphate modified release tablet 15mg every twelve hours. Suggested starting dose when moving from step 2 to step 3 is morphine sulphate normal release 5-10mg every 4 hours (consider lower dose in frail/elderly).

NB: The preferred option is to titrate with a short acting opioid and then convert to a long acting opioid. However patient circumstances sometimes do not allow this approach.

Alternatively Codeine 10mg = morphine sulphate 1mg.

Therefore 8 x 30mg codeine in 24 hours = 240mg codeine = 24 mg morphine with uncontrolled pain. In order to aim for pain relief, the 24 hour dose is increased by 30 - 50%, giving an increase to around 30mg morphine, administered as 15mg morphine sulphate modified release tablets twice daily.

4. Patient D, who has severe psychiatric problems and for whom a syringe driver is considered unsuitable, cannot take his morphine sulphate immediate release solution 15mg four hourly because of vomiting. It is decided to try a fentanyl patch. What dose would you advise?

The total daily oral dose of morphine is 90mg. There is no exact equivalence for the conversion of oral morphine to transdermal fentanyl because of the interindividual variability in absorption and distribution of medicine. The summary of product characteristics for transdermal fentanyl give a range of dose for conversion. Fentanyl is very potent and one fentanyl patch 25micrograms/hour changed every 72 hours is approximately equivalent to 90mg of oral morphine per day. Patients vary and care is required when starting fentanyl. Fentanyl patches are only suitable for stable pain. Therapeutic plasma concentrations of fentanyl can take between 12 and 24 hours to reach following initial application, (12 hours to therapeutic effect, 48 hours to steady state), therefore administration of oral morphine solution requires to continue for at least 24 hours.

An antiemetic may also be required and this may depend on the cause of emesis. (see chapter 4).

Half laxative dose and adjust accordingly.
Suggested answers

Activity 2

1. What recommendation would you make on Mrs A’s medication in relation to:
choice and dose of analgesic
As the patient is currently taking analgesics on Step 1 of the WHO ladder, inclusion of a medicine
from Step 2 (weak opioids) is recommended. The medicines of choice would include codeine,
dihydrocodeine or co-codamol 30/500.
One option would be to introduce dihydrocodeine 30mg tablets four times daily initially,
since patient is already on regular paracetamol. The dihydrocodeine could be titrated up to a
maximum of 240mg daily, if required.

Any side-effects the patient may experience?
Dihydrocodeine and codeine are weak opioids and are likely to cause side-effects associated with
opioid use. The patient should be warned about:
• drowsiness and how this can affect her ability to perform tasks like driving.
• constipation being common, therefore routine use of a laxative is advised. The most
commonly used laxatives include a stimulant laxative (e.g. senna) and a faecal
softener (e.g. docusate) or a combination product (e.g. co-danthramer).

2. Consider the following questions.

Comment on the choice of analgesic.
Co-codamol 30/500mg is not a good choice of analgesic in this patient since it would provide
little, if any, additional benefit to dihydrocodeine. Both medicines are in Step 2 of the WHO
analgesic ladder; if there is inadequate benefit obtained at therapeutic doses of any medicine in
the class, then it is advisable to progress to Step 3.

What choice and dosage of analgesic would you recommend to the GP in this situation?
Regular doses of morphine sulphate immediate release (tablets or liquid) 5-10mg every four
hours and when required for breakthrough pain. Note that in the elderly and patients with
impaired renal function, a lower initial dose of morphine should be used e.g. 2-5mg; such
patients may also require a longer dosage interval. Although weak opioids should be stopped
when commencing a strong opioid, it is recommended that a non-opioid analgesic be continued.
How would Mrs A's analgesic requirements be determined and what changes are required when this has been done?

The dosage should be reviewed every 24 hours and adjusted until adequate analgesia is achieved. Dose increases of the order of 30-50% or in line with the total daily dose in the previous 24 hours (i.e. regular doses plus breakthrough) should be made. It is then possible to calculate the total daily morphine dose that is required by the patient, by adding up all the four hourly and breakthrough doses taken, and converting to a suitable dose of a modified release capsule or tablet (given once or twice daily). The 'as required' dose of morphine should be approximately one sixth (1/6th) of the total daily dosage of modified release morphine being taken. For example, if the patient was taking morphine sulphate modified release tablets 30mg twice daily, the 'as required' dosage of morphine sulphate immediate release would be 60mg ÷ 6 = 10mg, prescribed 'as required for breakthrough pain'.

3. What recommendations would you make on Mrs A's medication in relation to alternative medicines, in view of Mrs A's nausea and vomiting

The oral route is no longer suitable. A syringe driver is an effective means of delivering a small volume continuous subcutaneous infusion. The most appropriate analgesic for subcutaneous administration in the syringe driver would be diamorphine, since it is highly soluble, and hence can be given in a small volume of solution. It may be possible to discontinue the syringe driver after a few days, on resolution of her nausea and vomiting, and restart Mrs A on oral therapy.

When converting from oral morphine to subcutaneous (SC) diamorphine, the 3 : 1 rule is applied, i.e. 3mg oral morphine = 1mg SC diamorphine.

Mrs A is currently taking morphine sulphate modified release 30mg twice daily. The initial dosage of diamorphine is calculated as follows:

Total daily dosage of oral morphine = 30mg x 2 = 60mg daily.
Equivalent dose of SC diamorphine = 60mg ÷ 3 = 20mg over 24 hours.
Mrs A would therefore require approximately 20mg of diamorphine over 24 hours.
An antiemetic could be added to the syringe driver. It is essential to check for compatibilities. (See Medicine Delivery Systems section on page 172).

Note that fentanyl patches would not be suitable for Mrs A as an alternative to oral morphine, as they have a long lag time to onset of action, and hence should be reserved for patients with stable pain.

An NSAID and paracetamol could be given rectally if still required.

Suitable breakthrough analgesia?

It is essential that a dose of diamorphine is also prescribed for breakthrough pain. This is calculated as approximately one sixth of the total daily dosage of diamorphine, so 2.5mg would be a reasonable breakthrough dose in this patient. Note that the calculated dose of diamorphine may be rounded up or down, to ensure that the dose can be measured accurately. In some areas, avoidance of decimal points for opioid doses is advocated to minimise the risk of errors in dosage, with the calculated dose rounded up or down as appropriate.
Additional References

- BNF Section on Palliative Care (most recent edition).
Chapter 3  Difficult to control pain
Objectives

On completion of this chapter you should be able to:

- list pains which are considered ‘difficult to control’
- define opioid toxicity and its management
- outline treatment choices and how these are initiated for difficult to control pain
- list pharmaceutical issues relevant in difficult to control pain.
Chapter 3
Difficult to control pain

Description of symptom
Pain is a complex symptom and is experienced by around 70% of patients with advanced cancer. When pain does not respond to the conventional approach to treating chronic pain, using the WHO analgesic ladder it can be defined a ‘difficult to control’ pain. Although some difficult to control pains can be predicted (see table below) others cannot be easily predicted. A range of approaches and medicines can be considered for difficult to control pain and include opioid rotation, adjuvant analgesics (including NMDA receptor antagonists) and anaesthetic procedures.

Summary of difficult to control pain

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain</td>
<td>• optimise opioids initially</td>
</tr>
<tr>
<td></td>
<td>• increase of modified release opioids is not always indicated as it may lead to opioid toxicity</td>
</tr>
<tr>
<td></td>
<td>• trial of adjuvant analgesics</td>
</tr>
<tr>
<td></td>
<td>• non drug methods (e.g. TENS, acupuncture)</td>
</tr>
<tr>
<td></td>
<td>• tumour infiltrating or compressing nervous tissue either centrally or peripherally</td>
</tr>
<tr>
<td></td>
<td>• surgery</td>
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<td></td>
<td>• radiotherapy</td>
</tr>
<tr>
<td></td>
<td>• chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• non-cancer causes e.g. viral infection</td>
</tr>
<tr>
<td></td>
<td>• diabetic peripheral neuropathy</td>
</tr>
<tr>
<td>Incident pain: transient</td>
<td>• anticipate incident pain with use of breakthrough doses, particularly short acting fentanyl</td>
</tr>
<tr>
<td>precipitated by a voluntary action</td>
<td>• 50% nitrous oxide/50% oxygen</td>
</tr>
<tr>
<td></td>
<td>• non drug methods (e.g. physiotherapy, surgery)</td>
</tr>
<tr>
<td>Visceral pain: poorly</td>
<td>• optimise opioids and Step 1 analgesics</td>
</tr>
<tr>
<td>localised and difficult to</td>
<td>• nerve blocks</td>
</tr>
<tr>
<td>describe</td>
<td></td>
</tr>
<tr>
<td>Complex/difficult to control pain</td>
<td>• spinal administration of opioids (see Chapter 13 page 181)</td>
</tr>
<tr>
<td>Localised bone pain</td>
<td>• consider radiotherapy</td>
</tr>
</tbody>
</table>
Adjuvant Analgesics
These are medicines with a primary indication other than pain but are analgesic in some painful conditions. A wide range of drugs are used in clinical practice including tricyclic antidepressants, anticonvulsants, steroids, NSAIDs and COX II inhibitors, bisphosphonates, antispasmodics, muscle relaxants and NMDA receptor antagonists. Many of these drugs are being used out with their licensed indication.

Tricyclic Antidepressants and Anticonvulsants
Amitriptyline is the most commonly used tricyclic antidepressant although unlicensed for this indication. It is thought to exert its analgesic action through blockade of presynaptic uptake of noradrenaline and serotonin. The starting dose is 10-25mg at night titrating upwards as needed. Relief of pain may not occur for several days. The antidepressant effect may take longer, anything up to several weeks to develop.

Gabapentin is an anticonvulsant drug with GABA receptor activity that is licensed for the treatment of neuropathic pain. Unlike many other anticonvulsants, it causes very few drug interactions and is generally well tolerated by patients. In the very frail or elderly, tolerability is improved by commencing at a very low dose and titrating up slowly.

The choice of agent is determined by the co-morbidities, concomitant medication and medication side-effects. Tricyclic antidepressants and anticonvulsants both have a number needed to treat of around 3 (i.e. you need to treat three patients to obtain evidence of benefit in one patient). Newer agents such as pregabalin require to have comparison studies with existing therapies. Pregabalin has been approved by the Scottish Medicines Consortium (SMC) for restricted use for peripheral neuropathic pain.

NMDA Receptor Antagonists
Activated NMDA receptors are involved in the wind-up phenomenon that is associated with difficult to control pain. The presence of allodynia (painful sensation as a result of non-painful stimulus), hyperalgesia (painful response to painful stimuli is magnified) and hyperpathia (prolongation of pain response) are indicative of the wind-up phenomenon and are responsive to NMDA receptor antagonists. Ketamine and methadone have NMDA receptor antagonist properties. They should be initiated under specialist palliative medical supervision only.

Corticosteroids
Dexamethasone can be used for raised intracranial pressure, spinal cord compression or liver capsular pain. The response is reviewed and the aim is to gradually reduce to the lowest effective dose. Monitoring for side-effects and appropriate action is required e.g. gastric protection, monitoring of blood glucose, mobility issues related to myopathy.

NSAIDs and COX II Inhibitors
These drugs exert their effect by the inhibition of prostaglandin synthesis. They are often effective in the treatment of bone pain. Side-effects and co-morbidities influence the choice of agent and care must be taken in patients with pre-existing cardiac or renal disease. Gastric protection may be required. Additional guidance is contained in SIGN guideline 106, Control of pain in adults with cancer, Section 6.1.1.
Radiotherapy
Radiotherapy can give partial or complete relief of pain from bone metastases in some patients, and as a consequence, improved motility. It should be considered when bone pain is relatively localised and is difficult to control with pharmacological management. For further details, refer to section 8.2 in SIGN guideline No 106 Control of pain in adults with cancer, and to section 6.2 for a comparison between bisphosphonates and radiotherapy of Numbers Needed to Treat (NNTs) to achieve analgesia in patients with bone pain.

Radioisotopes
The aim of treatment with radioisotopes is usually to shrink bone tumour(s) which prevents any such tumours from pressing on nerves and also may destroy areas of tumour(s), allowing bone to repair and strengthen. This may be an option where metastases are widespread and external beam radiotherapy is not an option. An example here would be the injection of strontium-89.

Bisphosphonates
Bisphosphonates may be considered for the management of bone pain, which is not adequately responding to other analgesics or radiotherapy or where radiotherapy is not an option. Bisphosphonates have a high affinity for bone, absorbing calcium phosphate, suppressing the function of mature osteoclasts and preventing formation of mature osteoclasts. They remain within the skeleton for long periods of time. Their use is twofold in that they can be used to treat pain and also for prevention of skeletal related events. Bisphosphonates may take several weeks before analgesia is experienced. Maintenance analgesia with opioids may require to be reduced when this occurs. There is insufficient evidence to support the use of bisphosphonates first line for bone pain and limited evidence supporting choice, dose or route for specific primary tumours. There are a number of potentially serious adverse effects which are referred to in section 6.2 of SIGN guidelines 106 Control of pain in adults with cancer.

Muscle Relaxants
Benzodiazepines such as diazepam or midazolam are most commonly used. The muscle relaxant dose is similar to the anxiolytic dose. Baclofen is useful in treating muscle spasticity. Baclofen is an agonist which activates GABA receptors. GABA receptors are found throughout the spinal cord.

Antispasmodics
Hyoscine butylbromide can be used to relieve gastro-intestinal colic, which is poorly responsive to opioids.

Lidocaine
Lidocaine stabilises membranes by inhibiting sodium channels, decreasing excitability and slowing conduction velocity. The application of transdermal lidocaine 5% plasters may be helpful in localised neuropathic pain. A licensed preparation has recently been marketed although it is licensed only for the relief of neuropathic pain associated with previous herpes zoster infection, and has been accepted by SMC for restricted use when first-line therapies for this indication are not tolerated or ineffective.
Cannabinoids
There is little evidence for the use of cannabinoids in the management of cancer pain. The side-effects outweigh the benefits and cannabinoids are not recommended for use. There may be some evidence emerging for further investigation of cannabinoids in the treatment of neuropathic pain.

Opioid Toxicity
Patients can show signs of opioid toxicity with any opioid. Signs include agitation, confusion, sedation, auditory and visual hallucinations, seeing shadows at the periphery of the visual field, vivid dreams and myoclonus (contraction of muscles seen as jerking). Severe toxicity leads to reduced consciousness and respiratory depression. Patients on opioids for moderate to severe pain should be monitored closely for signs of opioid toxicity.

Causes of opioid toxicity include deteriorating renal function, inadequate hydration (simply not drinking sufficient fluid) and using an opioid for an “opioid poorly responsive” pain, in addition to commencing on too high a dose or titrating the dose up too quickly.

Opioid toxicity should be managed by:
- reducing the dose of opioid (the dose reduction depends on clinical strategy, renal function, etc.) e.g. 30-50%
- ensuring the patient is adequately hydrated
- treating the agitation and confusion with haloperidol
- a thorough holistic reassessment of the person’s pain and its management.

Opioid rotation should be considered if symptoms of opioid toxicity persist despite these measures, preventing optimisation of the morphine dose.

Opioid rotation (switch)
Despite the optimal use of morphine and aggressive attempts to prevent adverse effects, some patients may develop intolerable toxicity and may benefit from opioid rotation. The term opioid rotation is used to describe a switch from one opioid to another with the aim to produce improved analgesia and reduced side-effects. Opioid rotation (or opioid switch) should be considered for patients with opioid-responsive pain whose morphine or diamorphine dose is unable to be increased due to toxicity, when patients have symptoms such as agitation, confusion, sedation, hallucinations or myoclonus.

Opioids for moderate to severe pain which could be considered are:
- fentanyl
- oxycodone
- hydromorphone (palliative care input)
- methadone (initiated under specialist palliative medical supervision only)
- alfentanil (initiated under specialist palliative medical supervision only).
The choice may depend on patient factors such as ability to take medicines orally, renal function and concomitant symptoms (e.g. constipation). At the low dose range of morphine, there is a restricted range of alternative opioids which can be considered due to strengths of dosage forms available. Equally problems may occur at higher doses because of the tablet burden for breakthrough analgesia.

Response to opioid rotation cannot be predicted and therefore, as with any analgesic regimen, regular review and assessment is essential. Dose equivalents are also approximate and careful assessment is required to ensure adequate titration up or down of the second line opioid. Dosage equivalents may change between the same medicines, depending on the direction of switch. Further information on opioid rotation and the limitations of opioid dose conversions may be found in SIGN guideline 106 Control of pain in adults with cancer, Sections 7.4 and 7.5.

**Breakthrough Pain**

Breakthrough pain is the term used to describe a transient flare of pain that is moderate to severe in intensity, arising on a background of controlled pain. This includes:

**Spontaneous breakthrough pain** – unpredictable acute exacerbations of pain above baseline pain, which is usually controlled by an opioid regimen.

Patients receiving a maintenance regimen of opioid should have a rescue dose of immediate release opioid prescribed for breakthrough pain. This is usually one sixth of the total daily dose of maintenance opioid although the proportion may vary, some patients requiring less and some more. Titration of breakthrough dose may be appropriate to avoid the possibility of opioid toxicity. Patients who regularly require more than two breakthrough doses of opioid in 24 hours, require to have their pain reassessed. If the pain is opioid responsive the maintenance opioid dose can be increased either by 30-50% if at low doses, or by adding the amount of breakthrough opioid taken in 24 hours to the maintenance dose.

Common breakthrough medications are immediate release oral forms of morphine or oxycodone and less commonly used is oral hydromorphone. Injectable preparations used are diamorphine, oxycodone, morphine, hydromorphine (unlicensed) and alfentanil.

Transmucosal fentanyl citrate lozenges (Actiq®) were developed for the treatment of breakthrough pain. The dose of lozenge required is titrated for the individual patient and bears no relation to the maintenance dose of opioid. Maximum plasma concentrations of fentanyl are achieved between 20 and 40 minutes. The lozenge requires to be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximising the amount of mucosal exposure to the product. This process may require some effort over a 15 minute period. The oral mucosa requires to be moist. Dry mouth is a common problem in palliative care patients and the oral mucosa may require to be moistened. These lozenges may be useful for ‘incident pain’ relief (see later). Alternative formulations of fentanyl, buccal (Effentora®) and sublingual (Abstral®) tablets may enable greater choice for treating
breakthrough pain, although none of these fentanyl preparations are bioequivalent so should be prescribed by brand name, as the dose titration phases are complex.

**Incident pain** – breakthrough pain which occurs as the result of a voluntary action e.g. pain on dressing change, pain on movement.

Incident pain is usually of a sudden, anticipated onset and relatively short lived nature. The characteristics of the ideal medication for incident pain would be to have a rapid onset of action with an effective period of action of approximately 30 minutes, and not add significantly to typical opioid side-effects. Medication administered for incident pain should not be added to the maintenance opioid dose requirements to manage baseline pain, otherwise dose escalation with subsequent opioid toxicity will occur. Immediate release oral formulations of opioids are commonly used (see above under breakthrough pain). An unlicensed product, alfentanil spray, has been manufactured by a hospital pharmacy department and may be useful for the treatment of incident pain or IV alfentanil can be given sublingually.

**End of dose pain** - pain which returns before the next dose of opioid is due. Monitoring and assessment of pain and analgesic requirements will reveal a consistent pattern, indicating end of dose failure of medication. An increase in the dose of around the clock medication will address end of dose failure.

The pharmacokinetics of opioids vary between individuals. A very few patients, who have an opioid responsive pain, require administration of opioids more frequently than is usually expected e.g. fentanyl patches may require to be applied every 48 hours rather than every 72 hours.

### The Patient’s View: Vicky

Vicky was diagnosed with breast cancer some years ago. These are her experiences of dealing with her pain.

“In late August I saw a GP again and asked for amitriptyline, which a rheumatologist friend had suggested. (He had also suggested gabapentin but for some reason the GP was reluctant to give it to me). Thirty milligram’s at night helped me to sleep a little. I began to hope that better sleep would lead to some improvement. However, I also began to feel pain down my right side between my ribs and my hip, especially if I leaned or twisted to the right.”

“Then, in early September, I turned over in bed and suffered excruciating pain. This rendered me completely immobile for several minutes. This was the start of increasingly severe pain. Over the next couple of months the skin on the right side of my torso became very sore. I could not bear anything to touch it. I started to wear pinafore dresses as I could not wear trousers, skirts, tights or anything with a waistband. If I leant against a cushion the pressure exerted by a fold in my t-shirt could cause intense pain. I slept on top of a duvet folded in half to reduce pressure on my back and side at night. Sleep was difficult. If I walked for more than two or three minutes I felt as if I was being suspended from a hot rod which skewered me from back to front. I visited the GP every two to three weeks; I received sympathy, but no additional pain relief. (One doctor said: “It must be very depressing to have been in pain for such a long time”. But depression was not the problem, pain was).”
“From September onwards I found it more and more painful to walk, and even to drive. In late October my rheumatology appointment came through. The consultant referred me to a physiotherapist, and I had my appointment a month later. The physiotherapist looked at my movements (almost non-existent in all directions) and listened carefully to what had happened. She began by saying, “I can see that you are in a great deal of pain. You don’t need to try to convince me of it”. This was the first acknowledgement from a health professional that my pain was bad. I almost cried. By now my back was curved to the right in a shallow “c” shape and the muscles were in constant spasm. The physiotherapist recommended hydrotherapy. I had 10 weeks of treatment, three times a week. It helped my lower back (which had early arthritis) but not the main area of pain, which was in the middle of my back, through the front and round my side.”

“I continued to see the doctor to get prescriptions renewed. One doctor touched my back while he was looking at it, and tears began streaming down my face. I had not cried before while seeing a GP; perhaps it would have been better if I had. He looked at me and said “we need to deal with this”, and prescribed tramadol (8 x 50mg a day). Meanwhile, the physiotherapist referred me to the pain clinic. By Christmas I was on daily doses of gabapentin (900 mg), amitriptyline (30 mg) and tramadol (400 mg). The pain became slightly more bearable.”

“In February the pain consultant gave me a number of facet joint injections in my spine to see if they would help. This did not, and in the following 10 days my back swelled and I was in intense pain. During the procedure the diagnostic x-ray showed that part of the lower edge of one vertebra was missing, so the consultant referred me back to oncology. A month later the CT, bone and liver scans and chest x-ray showed that half the vertebra was now missing, and that metastatic breast cancer had spread throughout my bones, liver and abdomen. During that consultation my oncologist said, “You have been in very severe pain for a long time. We can do something to help.”

“Having my pain acknowledged by someone who is experienced at recognising it was very important. It allowed me to accept that my pain was much worse than that of the many people who had sympathised with my bad back by telling me about theirs. At times I had wondered whether I was finding it difficult to deal with the pain because I was so tired from lack of sleep, or whether I was just a wimp, even though previously my ability to tolerate pain had always been good.”

“I think my trips to the doctor every three weeks to get a new prescription should have “flagged up” that I was in severe pain. Perhaps it was overlooked because I saw so many doctors in the practice over the first few months, and only began to insist on seeing the same one (the one who had given me tramadol) about eight months after the onset of the pain. Perhaps I did not complain enough about the pain. Perhaps I should have cried. Perhaps I should have realised that it is not normal to be unable to walk for more than a few minutes at a time.”
“But being in pain means that you constantly adjust your perception of what is “normal” and you adapt to the “normality” of a life in pain. If you have a longer period of sleep than usual, or wake only five times a night instead of six or seven, then you feel pleased, slightly more energetic, and even hopeful that things might be improving.”

“I also found it difficult to moan to people about the pain. If asked how my back was, I would say that the trend was probably slow improvement. Nobody wanted to hear that it was getting worse, so I did not tell them. Only close friends who could see the pain lines deepening on my face and saw how I struggled to do anything knew that the pain was, in fact, terrible.”

“On the day of my cancer diagnosis I had my first bisphosphonate injection (Zometa, which I still have every three to four weeks) and a week later I had a single high dose radiotherapy treatment to the middle of my spine. At last, the pain began to decrease.”

“Now, a year later, I take only three tramadol, three gabapentin and 10mg of amitriptyline each day. The pain is sufficiently controlled for me to be able to walk several miles, and even to do a little light gardening, but I can still hurt myself easily, I can lift very little, and I have to be careful of my spine. (A recent bone scan showed that the bone density has increased significantly so that my spine no longer flexes sideways as much, which means that the pain in my side caused by squeezed nerves is much reduced).”

“It is ironic that only after I was diagnosed with terminal cancer was anyone able to reduce the pain sufficiently for me to resume a relatively normal life.”

Now read Section 3 ‘Difficult pain’ in The ABC of Palliative Care (second edition) included with this pack. Also read the following article. Fallon M. Opioid rotation: does it have a role? (editorial), Palliative Medicine 1997; 11:177-178 and SIGN guideline 106 Control of pain in adults with cancer, Treatment with non-opioid drugs, pages 18-34.
Opioid rotation: does it have a role?

Opioid rotation is the term given to a switch from one opioid drug to another. The aim is to achieve a better balance between analgesia and side-effects. The keystone to the rationale behind opioid rotation is incomplete cross-tolerance.

Tolerance is the phenomenon whereby the dose of a drug needs to be increased to achieve the same effect. It is also described as a shift to the right in the dose-response curve. Selective tolerance describes stable analgesia accompanied by diminution of side-effects.

Tolerance is a complex phenomenon and there has been some controversy as to how often it occurs with systemic opioids in the clinical management of cancer pain. While tolerance occurs to adverse effects of opioids, clinically relevant tolerance to the analgesic effects is thought to be uncommon.

Cross-tolerance describes the phenomenon of tolerance to one drug resulting in tolerance to another drug. Incomplete cross-tolerance may apply to wanted effects, e.g. analgesia, and unwanted effects, e.g. sedation, nausea, vomiting, dry mouth and constipation.

The benefit of a switch from one opioid to another opioid depends on cross-tolerance to the analgesic effects being less than cross-tolerance to the adverse effects.

There is clinical evidence that cross-tolerance occurs; the patient with prior exposure to opioids is less susceptible to significant opioid-initiation adverse effects. Incomplete cross-tolerance is evidenced in the patient who has a recurrence of the initiation side-effects of opioids after switching opioids. Subclinical or even clinical opioid withdrawal symptoms on switching from one opioid to another opioid also reflects incomplete cross-tolerance. At a cellular level the theories of incomplete cross-tolerance are complex but include binding to different receptor subtypes and the use of different secondary messenger systems by different opioids.

The clinical advantage of opioid rotation lies in the possibility of incomplete cross-tolerance favouring analgesia more than adverse effects. The disadvantage is that the clinician cannot know in advance whether an opioid switch will increase analgesia more than adverse effects. In addition, the equianalgesic dose of the alternative opioid chosen may be uncertain: it will depend on the opioids being used, the individual patient, and the degree of cross-tolerance, as well as the nature of the pain. The patient in the higher dose range is potentially at greater risk of the equianalgesic dose being several-fold different than expected.

Evidence that tables of equianalgesic dose conversions differ from the clinical situation in opioid rotation comes from clinical observations. Methadone has been used in opioid rotation, particularly in North America, but a further complication of a methadone switch is the emerging evidence for its NMDA (N-methyl-D-aspartate) antagonist activity.

Consideration of the place of opioid rotation in the management of cancer pain naturally leads to the concept of opioid responsiveness. One of the commonest reasons for switching opioids is poorly controlled pain with unacceptable adverse effects from the current opioid. It is believed that opioid responsiveness should not be judged on the analgesic response to one opioid and should only be assessed after a trial of at least one alternative opioid.

To avoid unnecessary complication in the management of cancer pain it is important to examine some basic clinical facts. Morphine appears to have no clinically relevant ceiling effect to analgesia; hence there is no specific point of pain relief or inadequate pain relief with morphine but a point when adverse effects mean further titration of morphine is not possible. Whether unacceptable adverse effects occur before adequate analgesia is achieved depends on patient, drug and pain-related factors.
Editorial

An anxious patient who uses morphine as an anaesthetizer is likely to reach unacceptable adverse effects before adequate analgesia. Similarly, the inexpert use of morphine, with inappropriately rapid titration, lack of attention to prevention and management of adverse effects and inadequate use of adjuvant analgesics will result in unacceptable adverse effects before adequate analgesia is reached.

Some pains are less responsive to opioids than others. Neuropathic pain is commonly quoted as being opioid poorly-responsive, but there is substantial animal experimental evidence that neuropathic pain can be controlled by opioids. However, in the clinical situation large doses are often required and adverse effects may become unacceptable before analgesia is reached rather than there being any predetermined absence of opioid-responsiveness.

It is of some concern that several of the reports in the literature advocating opioid rotation, have done so on the basis of pain in the confused, agitated, and evidently opioid-toxic patient. A less complicated and more predictable approach would be to:

- review the clinical situation and pain syndrome;
- review adjuvant analgesics;
- decrease the opioid dose avoiding sustained release preparations;
- deal with the altered sensorium secondary to opioid toxicity using haloperidol;
- correct any contributing abnormal biochemistry; opioid toxic patients simply do not drink enough.

At present none of the other strong opioid analogues has been shown to have advantages which would make it preferable to morphine for routine use. However there is evidence that a failure to respond to one opioid does not mean failure to respond to all opioids and opioid rotation may allow pain control to be achieved without disabling side-effects.

The most frequently used alternative opioids in the UK are fentanyl, methadone and phenazocine; oxycodone and hydromorphone are alternatives elsewhere. Methadone is a difficult drug to use for the nonspecialist; titration can be difficult and equianalgesic conversion can be complex. Fentanyl is an interesting drug and more precise information is awaited from clinical trials, however it is not suitable in the unstable pain syndrome. Phenazocine is a useful alternative to morphine, particularly if dysphoria exists, but it is not available outside the UK. It is important to remember that some of the alternatives to morphine are much more potent than morphine.

An active quest for safe, more efficient analgesia, with a better balance between analgesia and unwanted effects is our universal aim. Opioids, of which morphine is the most commonly used, are the mainstay of moderate to severe cancer pain management. Opioid responsiveness is a continuum which can be affected by many factors, but inappropriate assessment and prescribing can shift a patient to the less responsive end of the continuum. Basic reassessment should be a prerequisite before any thought is given to opioid rotation.

Opioid responsiveness should not always be based on one opioid and in some situations an opioid switch can result in a better balance between wanted and unwanted effects because of incomplete cross-tolerance. Opioid rotation will have a place in the management of a selected group of patients. We need to examine the pharmacodynamic effects of the different opioids in the clinical setting, but at present this information is lacking.

Dr Marie Fallon, Beatson Oncology Centre, University of Glasgow, Western Infirmary, Glasgow, UK.

References
Summary of articles

- Pain control should be achieved by using the WHO analgesic ladder in around 80% of patients.
- Some types of pain respond poorly to opioids and in these situations the use of an adjuvant analgesic should be considered.
- Neuropathic pain may be produced by a tumour infiltrating or compressing nervous tissue, either centrally or peripherally, and may also be a result of surgery, radiotherapy, chemotherapy, or viral infection.
- Incident pain is transient pain precipitated by a voluntary action, such as weight bearing or movement in patients with pain due to bone metastases.
- Management of incident pain relies on thorough assessment, treatment of the underlying cause if possible (such as radiotherapy for bone metastases), and optimisation of the analgesic regimen with opioids and appropriate adjuvants by means of ‘breakthrough doses’ in anticipation of pain.
- Visceral pain is often poorly localised and difficult to describe, which can make diagnosis of the underlying cause difficult.
- Visceral pain is initially managed with analgesic drugs; however, invasive techniques may be indicated at an early stage.
- There is evidence that a failure to respond to one opioid does not mean failure to respond to all opioids, and opioid rotation may allow pain control to be achieved without disabling side-effects.
- In neuropathic pain a trial of an opioid is always warranted.
- Many adjuvant analgesics are being used outwith their marketing authorisation and published evidence in cancer pain is lacking.
- Regular review of any analgesic regimen including assessment of side-effects is essential.
- A range of opioids (alternatives to morphine) are available for patients with an opioid-responsive pain in whom the morphine dose cannot be increased due to side-effects such as hallucinations or sedation.
- Anaesthetic procedures may be considered in a minority of patients with intolerable side-effects from opioids.
Activity 1

Answer the following questions:

Mrs B is a 57 year old woman with breast cancer and liver and bone metastases. Her medicines on admission are:

- Morphine sulphate modified release tablets 120mg twice daily
- Morphine sulphate immediate release solution 60mg hourly as required for breakthrough pain
- Senna 15mg orally once daily
- Cyclizine 50mg orally three times daily
- Diazepam 2mg orally three times daily
- Anastrozole 1mg orally once daily

She complains of breakthrough pain, constipation and a dry mouth. She is taking morphine sulphate solution for breakthrough pain but complains of increasing drowsiness.

1. Comment on Mrs B’s medication on admission and rationalise her medication.

2. Consider causes of her pain and suggest treatments.
3. After a few weeks at home Mrs B is readmitted for pain control. Her medicines on admission are now:

- Morphine sulphate modified release tablets 200mg twice daily
- Morphine sulphate immediate release solution 60mg hourly as required for breakthrough pain
- Co-danthramer strong 1 capsule twice daily
- Diazepam 2mg at night (reducing course)
- Diclofenac 50mg three times daily
- Anastrozole 1mg once daily

Mrs B says that the pain she complains of is relieved by the breakthrough doses of morphine sulphate solution. However she complains of drowsiness and visual disturbances when she requires more than two breakthrough doses in a day.

Recommend an analgesic, dose and initiation guidance for Mrs B’s pain control.
**Activity 2**

Complete the blanks in the following table of pharmaceutical care issues.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed analgesic medication history required</td>
<td>Obtain a thorough medication history, including analgesics tried and failed and reasons for failure</td>
<td>Documented medication history - this allows an informed approach to control of pain</td>
</tr>
<tr>
<td>Opioid toxicity with morphine (including sedation, hallucinations)</td>
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<tr>
<td>Neuropathic pain not responding to opioid</td>
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<tr>
<td>Patient/carer education regarding adjuvant analgesics</td>
<td></td>
<td></td>
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<tr>
<td>Liaison between healthcare settings</td>
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</table>
Suggested answers

Activity 1

1. Comment on Mrs B’s medication on admission and rationalise her medication.
   Consider regular simple analgesia e.g. Paracetamol 1g qds, has Mrs B previously tried this
   in addition to morphine or maybe she can’t manage 8 tablets per day? Morphine sulphate
   immediate release solution for breakthrough pain is too high (usual dose is one sixth of 24 hour
   dose). Therefore breakthrough dose should be 40mg hourly as required for breakthrough pain.
   Senna prescribed for constipation. Usually a combination of a stool softener and stimulant are
   required for opioid induced constipation.
   Patient on cyclizine, diazepam and morphine which can all cause drowsiness. Review indications
   and need for cyclizine and diazepam.
   Advice on mouthcare should be given to Mrs B as she is on an opioid (see mouthcare section).

2. Consider causes of her pain and suggest treatments.
   Do breakthrough doses of morphine help pain?
   Where is the pain(s)?
   Liver and bone metastases: consider an NSAID (e.g. diclofenac 50mg tds +/- gastroprotection;
   misoprostol or omeprazole), steroid or, if bone pain, bisphosphonate.

3. Recommend an analgesic, dose and initiation guidance for Mrs B’s pain control.
   Change to immediate release opioid and reduce dose (e.g. morphine sulphate immediate release
   solution 60mg every four hours). Encourage the intake of oral fluids to prevent dehydration.
   Review patient in terms of pain control and adverse effects, in particular drowsiness and
   hallucinations.
   If pain not controlled consider an opioid switch.
   Oxycodone, hydromorphone should be considered: pain not stable therefore transdermal
   fentanyl is not an option.
   The calculated dose of the new opioid is commonly reduced initially e.g. by 30%, then titrated
   according to response.
   Conversions based on 60mg morphine sulphate immediate release 4 hourly:
   • for oxycodone: oral morphine 2mg = oral oxycodone 1mg – oxycodone
     immediate release tablets or liquid 40mg po qds (oxycodone immediate release
     can be given 4-6 hourly).
   • for hydromorphone: oral morphine 10mg = oral hydromorphone 1.3mg –
     hydromorphone 7.8mg (3 x 2.6mg) immediate release capsules every 4 hours.
   Monitor patient response to analgesic regimen as well as for continued signs of opioid toxicity.
   Convert to modified release opioid when opioid requirements have been titrated and control of
   pain has been achieved.
## Activity 2

<table>
<thead>
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<th>Outcome</th>
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<td>• Documented medication history - this allows an informed approach to control of pain</td>
</tr>
</tbody>
</table>
| Opioid toxicity with morphine (including sedation, hallucinations) | Review and discontinue other sedating drugs  
Confirm renal function has not deteriorated; correct dehydration  
Change to short acting opioid and reduce dose  
Manage altered mental state with haloperidol  
Review pain syndrome - identify if there is a need for an adjuvant analgesic  
Consider an opioid switch if pain returns and/or signs of opioid toxicity persist  
Advise on choice and dose conversions for second line opioid | • Cancer pain controlled with appropriate analgesics |
| Neuropathic pain not responding to opioid | Ensure pain not responsive to opioid  
Advise on adjuvant analgesic for neuropathic pain (tricyclic antidepressant (TCA) or anticonvulsant) | • Pain managed with an appropriate dose and type of adjuvant analgesic  
• Initiation done to minimise side-effects |
| Patient/carer education regarding adjuvant analgesics | Advise on appropriate dose and titration to optimal dose  
Clarify use of TCAs/anticonvulsants as analgesics | • Patient/carer informed of adjuvant analgesic regimen with aim to have acceptable compliance  
• Supply patient information leaflet |
| Liaison between healthcare settings | Ensure information on unusual medicines (e.g. syringe drivers, ketamine) are passed on as patient moves between healthcare settings | • All relevant healthcare professionals (including pharmacists) are informed, allowing continuity of pharmaceutical care for patient |
References

Additional References
- Zeppetella G. Impact and management of breakthrough pain in cancer. Current opinion in supportive and palliative care 2009;3;1-6
Objectives

On completion of this chapter you should be able to:

- identify causes of nausea and vomiting in the palliative care patient group
- select appropriate medicines and route of administration to treat nausea and vomiting
- identify pharmaceutical care issues in the management of nausea and vomiting in the palliative care patient.
Chapter 4
Nausea and vomiting

Description of symptom
Nausea is an unpleasant feeling of the need to vomit, often accompanied by cold sweats, salivation, tachycardia and diarrhoea. Vomiting is the forceful expulsion of the gastric contents through the mouth.

Nausea and vomiting result from stimulation of the chemoreceptor trigger zone (CTZ) and/or the vomiting centre in the medulla oblongata. The vomiting centre is the final pathway for the initiation of vomiting and may be stimulated, via distinct neurological pathways, involving different neurotransmitters.

The choice of antiemetic will depend on the cause of the nausea and 25% of patients require more than one antiemetic. The concurrent use of prokinetic drugs and antimuscarinic drugs should be avoided as the final pathway for prokinetic drugs is cholinergic and therefore blocked by antimuscarinic drugs. Clinical pictures may aid the management of nausea and vomiting.

The choice of route will depend on the severity and duration of the nausea and vomiting. Prolonged nausea induces gastric stasis which reduces the absorption of oral medication. In the acute situation, antiemetics may be given by the subcutaneous route. When nausea and vomiting is prolonged, a continuous subcutaneous infusion delivered via a syringe driver/pump may be the best option.
Common reversible causes of nausea and vomiting in advanced cancer patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Patient advice and treatment options</th>
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<tbody>
<tr>
<td>Food smells</td>
<td>Avoid trigger foods</td>
</tr>
<tr>
<td>Food sight</td>
<td>Small well presented meals</td>
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<tr>
<td>Unpleasant odours</td>
<td>Well ventilated rooms</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Explanation, reassurance, benzodiazepines</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>Rehydration and bisphosphonate</td>
</tr>
<tr>
<td>Constipation</td>
<td>Rectal intervention, appropriate laxatives</td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
<td>Steroids</td>
</tr>
<tr>
<td>Pharyngeal irritation</td>
<td>Treat chest infection, treat oral thrush, aid expectoration</td>
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<tr>
<td>Intestinal obstruction</td>
<td>May require palliative surgery</td>
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<tr>
<td>Medicine induced</td>
<td>Review need for medicine, stop or replace with alternative medication</td>
</tr>
<tr>
<td>Gastric irritation</td>
<td>Stop medicine, consider gastroprotectant</td>
</tr>
</tbody>
</table>

Sites of action of common triggers of nausea and vomiting and receptors involved

Adapted from Palliative Care Formulary No 3. Edited Twycross R, Wilcock, A. palliativedrugs.com Ltd. 2007
The Patient’s View: Tony and Sue

Sue: “After his chemotherapy the hospital worried about Tony’s nausea and vomiting more than we did. I went out and bought a bucket and rubber gloves “just in case”. I never needed them; the medicine supplied did the trick: granisetron injections before and during the chemotherapy, dexamethasone for a few days post chemotherapy, and two tablets of domperidone (20 mg) four times a day.”

“Tony often woke up feeling sick but all his medicine along with a cup of tea and a slice of toast worked well, except when we were travelling. (It is also worth considering ginger, especially crystallised ginger or Seabands).”

Tony: “My nausea and vomiting were controlled well during my treatment and never caused me any real problems. What did surprise me was that early morning nausea and motion sickness persisted for about 18 months after treatment, and I became more prone to vertigo. A hearty breakfast usually got rid of the early morning nausea, although the motion sickness was more of a problem. Domperidone helped sometimes.”

Now read Section 7 Nausea and vomiting in the ABC of Palliative Care (second edition) included with this pack.
Summary of articles

- Up to 60% of patients with advanced cancer suffer from nausea, vomiting or retching at some time.
- There is an increased risk of nausea and vomiting in those under 65 years, women and those with tumours of breast or stomach.
- Symptoms may be due to conditions unrelated to the cancer.
- Reversible causes should be considered and treated appropriately.
- Careful assessment of the likely mechanism is necessary to select the appropriate drug.
- Persistent nausea can decrease gastric emptying and affect oral absorption of drugs. Drug therapy should be delivered via alternative routes until nausea abates.
- Non-pharmacological methods of treatment of nausea and vomiting are important. These include avoidance of food smells or unpleasant odours, diversion and relaxation.
- The causes of nausea and vomiting may be multifactorial, requiring combinations of drugs to treat.
- About 30% of patients who receive morphine feel nauseated during the first week of treatment.
- Intestinal obstruction, the symptoms of colic, continuous abdominal pain and vomiting usually occur together.
- With good or moderate control of nausea and vomiting, patients with intestinal obstruction can eat and drink as they choose, most favouring small and low residue meals.
- Treatment options in intestinal obstruction are:
  - palliative surgery
  - pharmacological treatment
  - nasogastric intubation
  - percutaneous venting gastrostomy.

Practice Points

Reflect on three patients with whom you have been involved who have suffered from either nausea or vomiting or both. Consider the following:
- What was the presumed cause of their symptoms?
- What treatment did they receive?
- Was the treatment effective?
- Were better options available and not used?
- Could the nausea or vomiting have been predicted?
- How could you have been more involved in the management of these patients?
### Activity 1

Complete the blanks in the following pharmaceutical care plan:

#### Nausea and Vomiting Pharmaceutical Care Plan

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reversible cause of vomiting</strong></td>
<td></td>
<td>• nausea/vomiting controlled</td>
</tr>
<tr>
<td><strong>Vomiting all medication</strong></td>
<td></td>
<td>• maintain control of symptoms</td>
</tr>
<tr>
<td><strong>Syringe driver/pump required</strong></td>
<td></td>
<td>• safe administration of drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• avoidance of anxiety</td>
</tr>
<tr>
<td><strong>Nausea from swallowing medication</strong></td>
<td>review prescription and stop non essential medicines review timing of medications</td>
<td></td>
</tr>
<tr>
<td><strong>Poor oral intake of fluid and food due to nausea or vomiting</strong></td>
<td>ensure access to appropriate mouth care/oral fluids</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea settled/reversible cause treated</strong></td>
<td></td>
<td>• minimise the use of invasive treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• avoid over or under-dosing the patient</td>
</tr>
<tr>
<td><strong>Chemotherapy induced vomiting</strong></td>
<td></td>
<td>• avoid predictable side-effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• avoid unnecessary medicine therapy</td>
</tr>
</tbody>
</table>
Mrs C is a 64 year old woman diagnosed with colon cancer six months previously. She had widespread liver metastases at diagnosis. She has called out her GP complaining of nausea, vomiting and loss of pain control. Her bowels have not moved for four days and her pain is worsening, as she cannot keep her medication down. Her current medication is:

- Morphine sulphate modified release tablets 30mg every 12 hours
- Morphine sulphate immediate release liquid 10mg as required for breakthrough pain
- Senna tablets two each night

Give advice on the necessary changes to Mrs C’s medication with regard to:

1. Treatment of the underlying cause of nausea and vomiting
2. Management of nausea and vomiting
3. Pain control.
### Suggested answers

**Activity 1**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible cause of vomiting</td>
<td>Ensure appropriate treatment of underlying cause</td>
<td>• nausea/vomiting controlled</td>
</tr>
<tr>
<td>Vomiting all medication</td>
<td>Ensure treatment of current symptoms available via non-oral route</td>
<td>• maintain control of symptoms</td>
</tr>
<tr>
<td>Syringe driver/pump required</td>
<td>Ensure drug suitable for subcutaneous administration</td>
<td>• safe administration of drugs</td>
</tr>
<tr>
<td></td>
<td>Check dose conversions are correct</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ensure drug combinations are compatible/stable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Explain rationale to patients/carers</td>
<td>• avoidance of anxiety</td>
</tr>
<tr>
<td>Nausea from swallowing medication</td>
<td>Review prescription and stop non essential medicines</td>
<td>• avoid treatment induced nausea</td>
</tr>
<tr>
<td></td>
<td>Review timing of medications</td>
<td></td>
</tr>
<tr>
<td>Poor oral intake of fluid and food due to nausea or vomiting</td>
<td>Ensure access to appropriate mouth care/oral fluids</td>
<td>• maintain oral hygiene and comfort</td>
</tr>
<tr>
<td>Nausea settled/reversible cause treated</td>
<td>Ensure restarting of oral medication at appropriate dosage</td>
<td>• minimise the use of invasive treatments</td>
</tr>
<tr>
<td></td>
<td>Check dose</td>
<td>• avoid over- or under-dosing the patient</td>
</tr>
<tr>
<td>Chemotherapy induced vomiting</td>
<td>Ensure appropriate regimen and course length prescribed</td>
<td>• avoid predictable side-effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• avoid unnecessary medicine therapy</td>
</tr>
</tbody>
</table>
Activity 2
Give advice on the necessary changes to Mrs C’s medication with regard to:
1. Treatment of the underlying cause of nausea and vomiting
   *Constipation due to inadequate laxative therapy with morphine is the most likely cause.*
   The bowels will need to be cleared using rectal treatments, giving a softening agent such as arachis oil or glycerin followed by a stimulant laxative. Bowel habit will need to be monitored and treated rectally until the patient is able to tolerate oral therapy. When this occurs add a softening laxative such as sodium docusate to the oral regimen or change to a combination product such as co-danthramer.

2. Management of nausea and vomiting
   *Use of a prokinetic agent would be advisable in this situation.* Metoclopramide will help the nausea and vomiting and will also accelerate gastro-intestinal transit. Metoclopramide should be administered via a non-oral route. Metoclopramide 20-60mg can be given subcutaneously over a 24 hour period. Once the nausea and vomiting is controlled the metoclopramide can then be swapped to the oral route and stopped once the underlying cause (constipation) has resolved. The possibility of total bowel obstruction should be excluded before commencing metoclopramide.

3. Pain control
   *Change analgesics to parenteral route.* Combine diamorphine with antiemetic and give over 24 hours as a continuous subcutaneous infusion. 60mg morphine orally each day is equivalent to 20mg diamorphine subcutaneously over 24 hours. Check that the combination of diamorphine and metoclopramide are compatible and that the appropriate diluent, water for injection, is used. Breakthrough pain relief should be given as a subcutaneous bolus of 2-5mg diamorphine until the patient is able to tolerate oral therapy again. Change back to the oral route, checking that the appropriate doses are used, when nausea and vomiting are controlled.
References


Additional References

- [http://www.nauseaandvomiting.co.uk/NAVRES001-2-NandV-general.htm](http://www.nauseaandvomiting.co.uk/NAVRES001-2-NandV-general.htm)
- [http://www.palliativedrugs.com](http://www.palliativedrugs.com)
Chapter 5  Other Gastro-intestinal symptoms
Objectives

On completion of this chapter you should be able to:

- list the main symptoms and causes of constipation and diarrhoea in palliative care patients
- describe common treatment strategies used to manage constipation and diarrhoea in palliative care patients
- respond to commonly presenting pharmaceutical care issues related to constipation or diarrhoea.
Chapter 5
Other Gastro-intestinal symptoms

Description of symptom
Constipation is the passage of hard stools less frequently than the patient’s own normal pattern. This condition provokes a wide range of concomitant symptoms including abdominal pain, bloating, flatulence, nausea, malaise, headache and halitosis.

Prevention of constipation is paramount, and should be anticipated in all patients taking opioids or anticholinergics, those who are bed-bound, or those with reduced fluid or fibre intake. Patients with little or no food and fluid intake continue to produce waste in the bowel (gut secretions, desquamation and bacteria) and can still become constipated.

If constipation is not treated it can develop into faecal impaction: the formation of a large faecal mass which is impossible to pass spontaneously. This may present with overflow diarrhoea and can lead to urinary incontinence in the elderly. The treatment of this depends on the level of discomfort the patient experiences and the place and level of care available. Oral treatment with Movicol sachets is possible, with almost all patients having successful treatment within three days. A more rapid response is possible with rectal laxatives. If these measures fail, or symptoms are very severe, then the patient may require to have their bowels manually evacuated, usually under sedation.

Approximate conversions
A 30ml dose of co-danthramer suspension is equivalent to:
- three co-danthrusate capsules
- 10ml co-danthramer forte suspension
- either 10ml senna syrup or two senna tablets with docusate 200mg
- either 10ml senna syrup or two senna tablets with 10ml lactulose
- three sachets of Movicol.

Notes
1. Dantron is restricted for treatment of constipation in the terminally ill.
2. Dantron containing products should be avoided with incontinent patients due to the risk of danthron burns.
3. Lactulose requires high fluid intake to be effective. Use can be limited by bloating and flatulence.

A new product, methylnaltrexone, has become available for use by the subcutaneous route to treat opioid induced constipation when response to usual laxative therapy has become insufficient. Constipation may be the result of a number of contributing factors and a full assessment will be required before considering use.

There is a lack of good quality evidence comparing the use of laxatives in palliative care patients and further research is needed in this area.
Diarrhoea is much less common than constipation in patients with advanced malignant disease. Less than 10% of those with cancer admitted to hospital or palliative care units have diarrhoea. Clostridium difficile enteritis should be considered in in-patients presenting with diarrhoea, particularly where recent antibiotic therapy has been administered and a stool sample obtained to confirm diagnosis. Standard treatments using oral metronidazole or vancomycin are used.

Antimotility antidiarrhoeal medicines comprise of the opioids and non-analgesic opioid derivatives loperamide and diphenoxylate. Loperamide is about three times more potent than diphenoxylate and 50 times more potent than codeine. It is longer acting and generally needs to be given only twice daily. Loperamide is limited in its ability to cross the blood brain barrier and is associated with fewer central side-effects than opioids.

Octreotide, a synthetic analogue of somatostatin with a longer duration of action, is occasionally used in parenterally intractable diarrhoea related to high output ileostomies, enterocolic fistula, AIDS, radiation, chemotherapy or bone marrow transplant.

Stoma care can be an integral part of caring for patients requiring surgical intervention for colorectal cancer. Urostomies may be in place to bypass non-functioning bladders. Further information on stoma care is available in the NES distance learning pack Management of lower gastro-intestinal disease). Administration of medicines for patients with a gastro-intestinal stoma requires consideration of formulation to aid absorption of the medicine(s) e.g. avoidance of modified release preparations in patients with a high ileostomy.

Colic may be a distressing symptom to resolve. It may present as pain, which is either only partly or not responsive to opioids. Once any reversible causes of colic have been identified and resolved, treatment is usually with hyoscine butylbromide by the unlicensed subcutaneous route of administration because oral absorption is poor.

The Patient’s View: Tony and Sue
Sue: “The best advice here is to assume that someone is going to be constipated if they are taking 30 mg or more of codeine regularly. Two senna tablets every night whether Tony needed them or not proved to be a far better option than severe constipation (which seemed to occur every time he forgot to take them). All the normal advice about fibre, fluid etc, is still true, but actually eating the fibre was tricky sometimes.”

Now read Section 8 ‘Constipation, diarrhoea and intestinal obstruction’ in The ABC of Palliative Care (second edition) included with this pack.
Summary of articles

- Assessment is essential in patients with constipation to establish the nature of change of bowel habit.

- The most common causes of constipation are:
  - immobility
  - poor fluid and dietary intake
  - drugs (particularly opioids).

- Management of constipation includes:
  - laxative therapy (oral and/or rectal)
  - attention to other aspects of care, such as:
    › pain control
    › advice on diet
    › fluid intake
    › mobility
    › toileting is also essential.

- The aim of laxative therapy is to achieve comfortable defecation, rather than any particular frequency of evacuation.

- Although most laxatives are not very palatable, oral laxatives should be used whenever possible.

- The choice of laxative depends on the nature of the stools, the cause of the constipation, and acceptability to the patient.

- A distended rectum or colon can be a potent cause of agitation and pain in a dying patient. Evacuation of the rectum or colon with suppositories, alone or with an enema, can give complete relief of agitation.

- The use of opioids to treat the pain of constipation only makes the constipation, and ultimately the pain, worse and a vicious cycle ensues.

- Rectal laxatives are sometimes necessary for treating faecal impaction and for conditions such as spinal cord compression, when long term use may be necessary. They should not, however, be part of the regular treatment of every cancer patient with constipation.

- Care should be taken to distinguish true diarrhoea from overflow due to faecal impaction.

- The commonest cause of diarrhoea in patients with advanced disease is the use of laxatives.

- Symptomatic relief is generally achieved with non-specific antidiarrhoeal agents – loperamide or codeine.

- Rarely intractable diarrhoea may require a subcutaneous infusion of octreotide.
Practice Points
Visit www.aboutconstipation.org/site/about-constipation/treatment/stool-form-guide and look at the Bristol stool form scale. Think about how you could use this scale in your daily practice.

Activity 1
Answer the following questions:
Mr D is admitted to the local hospice with abdominal pain, flatulence and urinary incontinence. He has metastatic carcinoma of the lung and his current medication is as follows:
- Morphine sulphate controlled release tablets 60mg every 12 hours
- Morphine sulphate immediate release tablets 20mg hourly as required for breakthrough pain
- Ispaghula husk 3.5g sachet twice daily
- Diclofenac 50mg three times daily

Mr D reports that his bowels have not moved for five days, and that he would normally pass a motion every second day. Rectal examination is unremarkable. However a plain x-ray of the abdomen reveals large amounts of stools in the upper bowel.

1. What is the likely cause of Mr D’s discomfort?

2. What changes are required to the current laxative therapy? Why?

3. What counselling points would you cover with Mr D?
Mr D’s symptoms resolve during the subsequent five days and he is discharged to his own home. Eight weeks later Mr D is readmitted to the hospice complaining of persistent diarrhoea despite his general practitioner issuing a script for loperamide 4mg qds several days previously.

4. What management would you recommend and why?
Suggested answers

Activity 1

1. What is the likely cause of Mr D’s discomfort?

*Constipation.*

2. What changes are required to the current laxative therapy? Why?

*Bulk forming agents are stool normalisers rather than true laxatives. They are less helpful in cancer patients because of the volume of water required. They are unproven in severe constipation, and without adequate fluid intake there is a possibility of worsening an incipient obstruction. The ispaghula husk sachet should therefore be discontinued.*

*Opioids cause constipation by delaying passage of faeces through the gut, with resultant increase in absorption of electrolytes and water in the small intestine and colon. NSAIDs (e.g. diclofenac) may also exacerbate constipation.*

*Both a stimulant and softening laxative are required. Senna tablets two at night and docusate 200mg twice a day might be a suitable combination. Any bowel stimulant can cause abdominal colic and severe purgation; colic may be reduced by giving the total daily requirement in divided doses. Preparations containing the stimulant laxative Dantron® are not suitable for Mr D at present because his urinary incontinence puts him at increased risk of developing a danthron rash.*

3. What counselling points would you cover with Mr D?

*Explain the need for regular laxatives whilst taking an opioid.*

*Encourage increased fluid intake.*

*If colic occurs, spread the doses of senna throughout the day; if severe, reduce the dose.*

*Increase intake of dietary fibre and exercise if possible.*

4. What management would you recommend?

**Assessment**

*Establish Mr D’s current pattern of laxative use. Both overuse and underuse of laxatives can lead to diarrhoea due to either excessive purgation or faecal impaction with overflow diarrhoea. Recommend a rectal and abdominal examination and a plain X-ray of his abdomen.*

**Medication management**

*If faecal impaction is confirmed, stop the loperamide and treat using rectal laxatives. Hard impacted stools will require the use of a softening agent such as arachis oil enema first. This can be administered as a retention enema overnight, if necessary. Stimulant laxatives used alone at this point are likely to cause colic. Soft stools can then be evacuated using a stimulant such as phosphate enema. Adjust the oral laxative regime to improve compliance and maintain easy, regular defaecation. If faecal impaction is not the cause of diarrhoea, stop current laxatives and carry out further investigations.*
References:

Additional references:
- [http://www.palliativedrugs.com](http://www.palliativedrugs.com)
Chapter 6 Dyspnoea
Objectives

On completion of this chapter you should be able to:

- define the term dyspnoea
- list the main causes of dyspnoea in advanced disease
- outline the treatment of the main underlying causes
- describe the medications used for symptom control.
Chapter 6
Dyspnoea

Description of symptom
Dyspnoea is the term used to describe when people have difficulty in breathing easily. This can involve a physical impediment such as increased airways resistance or a non-physical trigger such as anxiety. Non-physical triggers can lead to increased respiratory drive which makes dyspnoea worse. The role of relaxation, correct positioning and breathing exercises are therefore important in the control of this symptom.

Dyspnoea can be a very complex symptom as the underlying causes are numerous and patients often have pre-existing lung disease. Treatment will involve identifying the causes of breathlessness and treating those that are reversible, then giving palliative treatments to alleviate remaining symptoms. Where previously diagnosed lung disease is present, it is important to ensure that treatment of this is optimised. The table lists those conditions which commonly cause dyspnoea in advanced disease and the appropriate treatment. The benefits of invasive treatments, or those which take a longer period of time to have an effect, need to be carefully considered in each patient to ensure that they will actually receive benefit.

Some causes of breathlessness

<table>
<thead>
<tr>
<th>Cause</th>
<th>Symptom/sign</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Low haemoglobin</td>
<td>Blood transfusion/iron supplement</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Chest pain</td>
<td>Chest drain/surgical intervention</td>
</tr>
<tr>
<td>Superior vena cava obstruction (SVCO)</td>
<td>Neck and facial swelling, headache, trunk and arm swelling, choking sensations</td>
<td>Steroids, chemotherapy, stenting</td>
</tr>
<tr>
<td>Infection</td>
<td>Increased C-reactive protein (CRP)/white cell count (WCC)</td>
<td>Antibiotic therapy</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>ECG changes</td>
<td>Antiarrhythmics</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>Chest pain</td>
<td>Anticoagulation, pain relief</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Wheeze</td>
<td>Bronchodilators, steroids</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Raised jugular venous pressure (JVP), poor ejection fraction</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Effusion (pleural/pericardial)</td>
<td></td>
<td>Pleural drain/pleurodesis</td>
</tr>
<tr>
<td>Stridor (is a symptom and not a diagnosis)</td>
<td>Noisy breathing</td>
<td>Heliox (mixture of helium 79% and oxygen 21%)</td>
</tr>
<tr>
<td>Excess secretions</td>
<td>Difficulty expectorating</td>
<td>Nebulised NaCl 0.9%</td>
</tr>
</tbody>
</table>
Now read Section 4 ‘Breathlessness, cough and other respiratory symptoms’ in *The ABC of Palliative Care* (second edition) included with this pack and refer to the article from Thorax. Ahmedzai S, Davis C. Nebulized Drugs in Palliative Care. Thorax 1997; 52(2): s 75-77.

Access at the link http://thorax.bmj.com/cgi/reprint/52/suppl_2/s56 using your Athens password, explained at the beginning of this document.
Summary of articles

- Breathlessness is an unpleasant sensation of being unable to breathe easily and has both physical and non-physical aspects.
- Up to 70% of patients with cancer will suffer breathlessness during the last six weeks of life.
- Several treatment options may have to be combined because of concomitant pre-existing diseases and exacerbating factors.
- Oxygen, anxiolytics and opioids all have a place in the therapy of breathlessness.
- Only a small number of patients should require continuous oxygen. For others, explanation combined with non-specific drug measures, especially anxiolytics, and possibly a bedside or hand-held fan can have dramatic effects.
- Benzodiazepines probably relieve breathlessness through anxiolytic and sedative effects and, possibly, muscle relaxation.
- If used inappropriately, opioids can induce respiratory depression. However, low dose oral opioids can improve breathlessness, sometimes dramatically, although the precise mechanism of action is unknown.
- Inhaled bronchodilators should be reserved for patients with reversible airways obstruction.
- Many of the treatment principles applied to cancer patients with dyspnoea can be applied to patients with non-malignant disease.
- The main conditions which would benefit from nebuliser therapy are dyspnoea, cough and pooling of saliva in the hypopharynx.
- Treatments are not evidence-based, but empirically derived from clinical experience.
- Patients should be sitting upright or at least at 45 degrees during nebulisation; administration to supine patients is inappropriate.
- Practical arrangements for nebulisers are very important and include:
  - education of patients and carers
  - instructions on cleaning
  - systems of maintenance
  - collection and delivery.
- The use of nebulised opioids to treat dyspnoea is still controversial.
- The use of nebulised local anaesthetics to treat cough should only be initiated by specialist teams.
### Activity 1
Complete the table below by providing actions that can be taken by a pharmacist to address potential problems.

**Dyspnoea**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea in a patient with a chemosensitive tumour</td>
<td>• Improve symptom control including dyspnoea</td>
<td></td>
</tr>
<tr>
<td>Wheeze present</td>
<td>• Improve wheeze and difficulty in breathing</td>
<td></td>
</tr>
<tr>
<td>Tachypnoea not relieved by relaxation or reassurance</td>
<td>• Reduce breathing rate to 15-20 breaths per minute</td>
<td></td>
</tr>
<tr>
<td>Anxiety induced</td>
<td>• Reduce number of attacks, reduce anxiety, improve any breathing difficulty</td>
<td></td>
</tr>
<tr>
<td>Patient hypoxic</td>
<td>• Improve sensation of dyspnoea</td>
<td></td>
</tr>
<tr>
<td>Issue</td>
<td>Action</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Cough triggering dyspnoea</td>
<td>Suppress cough</td>
<td></td>
</tr>
<tr>
<td>Secretions causing noisy breathing</td>
<td>Reduce oropharyngeal secretions</td>
<td></td>
</tr>
<tr>
<td>Patient too weak to use inhalers</td>
<td>Consider different delivery of medicine</td>
<td></td>
</tr>
<tr>
<td>Patient experiencing stridor</td>
<td>Manage breathing difficulty with effective gases/ nebulisers</td>
<td></td>
</tr>
<tr>
<td>Patient uses a nebuliser at home</td>
<td>Ensure use and function of device</td>
<td></td>
</tr>
</tbody>
</table>
Activity 2

Mr E’s wife reports that he is feeling very breathless and asks if there is anything he can take for this. On enquiry it appears that he has just been diagnosed with small cell lung cancer. They are both understandably upset and anxious about this. His patient medication record shows that he is taking:

- Beclomethasone 250 micrograms inhaler two puffs twice a day
- Salbutamol inhaler two puffs when required
- Salmeterol inhaler two puffs twice a day
- Furosemide 40mg in the morning
- Temazepam 10mg at night
- Diclofenac 75mg MR capsules twice a day

1. List the possible causes of breathlessness in Mr E.

2. What actions can a pharmacist take before referring Mr E back to a doctor?

3. If anxiety is the main trigger for Mr E’s breathlessness then how should this symptom be managed?
## Suggested answers

### Activity 1

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea in a patient with a chemosensitive tumour</td>
<td>Chemotherapy should reduce tumour bulk and improve symptoms</td>
<td>Improve symptom control including dyspnoea</td>
</tr>
<tr>
<td>Wheeze present</td>
<td>Trial of inhaled bronchodilator therapy</td>
<td>Improve wheeze and difficulty in breathing</td>
</tr>
<tr>
<td></td>
<td>Assess inhaler technique and choose appropriate device</td>
<td>Benefit from effective use</td>
</tr>
<tr>
<td>Tachypnoea not relieved by relaxation or reassurance</td>
<td>Trial of strong opioid. Low dose oral morphine regularly</td>
<td>Reduce breathing rate to 15-20 breaths per minute</td>
</tr>
<tr>
<td>Anxiety induced</td>
<td>Trial of relaxation therapy, if unsuccessful trial of benzodiazepine e.g. sublingual (off-label use) lorazepam 500 micrograms (preferable to use blue scored tablets as are absorbed better sublingually than white tablets)</td>
<td>Reduce number of attacks, reduce anxiety, improve any breathing difficulty</td>
</tr>
<tr>
<td>Patient hypoxic</td>
<td>Trial of oxygen therapy</td>
<td>Improve sensation of dyspnoea</td>
</tr>
<tr>
<td>Cough triggering dyspnoea</td>
<td>Anti-tussive or nebulised NaCl 0.9%</td>
<td>Suppress cough</td>
</tr>
<tr>
<td>Secretions causing noisy breathing</td>
<td>Subcutaneous hyoscine butylbromide or hydrobromide</td>
<td>Reduce oropharyngeal secretions</td>
</tr>
<tr>
<td>Patient too weak to use inhalers</td>
<td>Nebuliser therapy</td>
<td>Consider different delivery of medicine</td>
</tr>
<tr>
<td>Patient experiencing stridor</td>
<td>Trial of Heliox, corticosteroids</td>
<td>Manage breathing difficulty with effective gases/nebulisers</td>
</tr>
<tr>
<td>Patient uses a nebuliser at home</td>
<td>Give advice on use, cleaning and maintenance</td>
<td>Ensure use and function of device</td>
</tr>
</tbody>
</table>
Activity 2

Main points:

**Mr E appears to have reversible airways disease from his medication history. He may be experiencing an exacerbation.** Often a course of oral steroids, e.g. prednisolone 40mg for seven days would be effective. **If the exacerbation is infective then a course of antibiotics would also be indicated.**

*He may require inhaler counselling to optimise current drug treatment.*

**The use of furosemide suggests the presence of congestive cardiac failure with pulmonary oedema which may be worsening.** In addition to this the diclofenac will cause fluid retention. **The dose of furosemide may need increased and the indication for diclofenac should be reviewed.**

**The primary lung tumour may have invaded the airways.** Superior vena cava obstruction is more common with lung tumours than with any other tumour type and can contribute to dyspnoea. **If SVCO is suspected the patient requires urgent referral for chemotherapy, steroids and or stenting.**

**Many patients with chronic disease are anaemic. Mr E should have his haemoglobin checked and receive a transfusion or iron supplementation dependent on the results.**

**Anxiety may lead to dyspnoea.** Counselling, relaxation exercises and or a trial of benzodiazepines could be offered.

**A cough may be triggering episodes and appropriate therapy should be commenced.**

References

Chapter 7 Nutrition and medication administration via enteral feeding tubes
Objectives

On completion of this chapter you should be able to:

• explain the cause of cachexia in advanced cancer

• outline the place of nutritional therapy

• give at least four examples of underlying causes of reduced nutritional intake and their treatment

• describe the use of medicines in anorexia and cachexia.
Chapter 7
Nutrition and medication administration via enteral feeding tubes

Nutrition is an important aspect of caring for patients with life limiting illness. Good nutrition support is essential, not only for meeting the body’s physical requirements but also because of the associated social, cultural and psychological benefits for patients. However, nutritional support measures should not be so invasive or unacceptable to the patient that they impair quality of life.

Cancer Cachexia

One of the most common concerns of relatives and patients is poor dietary intake and weight loss during the terminal stages. In advanced cancer more than 80% of patients will be cachectic, where the patient often suffers a combination of anorexia (loss of appetite with an associated decrease in intake), chronic nausea, asthenia (generalised weakness and tiring easily) and changes in body image. The mechanisms underlying cachexia involve major changes in metabolism including increased lipolysis, protein loss and gluconeogenesis. This change is brought about by production of cytokines by tumour tissue which trigger the catabolic state. For this reason, providing further nutrients is futile as the patient is unable to utilise these due to the underlying metabolic changes. In clinical trials aggressive nutrition has been shown to have no impact on survival or nutritional status and it is unclear whether nutritional support alters symptoms. In fact, by causing satiety, intensive nutrition can increase severity of anorexia and chronic nausea. Nutrition must therefore concentrate on patient comfort and preventing further, unnecessary nutritional deterioration.

Carers often feel responsible for weight loss associated with terminal disease. As the patients’ disease progresses, their desire to eat may dwindle and they may not wish to be fed at all. This leads to a high level of distress in carers and family. Any management strategy for cachexia must include explanation and practical suggestions for the carers:

- forcing the patient to eat does not improve their nutritional status or length of survival and may abolish the little appetite they have and increase nausea. This can also have a detrimental effect on patient carer relationship at this sensitive time
- nutrition should be led by the patient’s wishes
- encourage participation in family mealtimes whilst allowing the patient to eat what and when they wish
- provide well presented, small portions of high calorie foods
- provide assistance for eating and drinking when required
- compromise where patients are too weak or tired to participate in the full mealtime, with the patient joining for half the meal
- nutritional supplements, such as sip feeds, may be indicated where patients have difficulty with solid food stuffs.
Administration of sip feeds in palliative care may be difficult due to nausea and reduced appetite especially in the advanced stage. Advice regarding increasing the nutrient and calorie content of everyday foods is also of benefit.

Advice from a dietician can allay fears and provide practical support for providing appropriate nutrition. In addition to underlying metabolic changes, some patients have contributing factors which compromise their nutritional intake. The table below details common causes of reduced nutritional intake and the possible treatments.

NB: There is no article included in this section for you to read. Information and Patient Information Leaflets are included at www.palliativecareguidelines.scot.nhs.uk

<table>
<thead>
<tr>
<th>Causes of reduced nutritional intake</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or vomiting</td>
<td>Appropriate antiemetics</td>
</tr>
<tr>
<td>Pain</td>
<td>Appropriate analgesia (systemic and/or topical e.g. antacid with oxetacaine – unlicensed preparation available from Rosemount Pharmaceuticals)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Holistic approach to treating dyspnoea</td>
</tr>
<tr>
<td>Depression</td>
<td>Psychological support, antidepressants</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Advice on good oral hygiene, artificial saliva Review other medication</td>
</tr>
<tr>
<td>Infected, sore mouth</td>
<td>Appropriate antifungals or antibiotics Advice on good oral hygiene</td>
</tr>
<tr>
<td>Dysphagia (difficulty in swallowing)</td>
<td>Dietary advice Consider referral to speech and language therapist for neurological swallowing problems</td>
</tr>
<tr>
<td>Altered taste sensation</td>
<td>Dietary advice on different foods to try</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Counselling Anxiolytics as a last resort</td>
</tr>
</tbody>
</table>

When practical advice and treatment of underlying difficulties have not provided sufficient improvement, medicine treatment may offer some benefits. The balance of benefit against risk and the duration and onset of action of each medicine class must be considered (see the table on the following page). The effect of these medicines must be closely monitored and the medicine withdrawn if a positive effect is no longer apparent.
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Corticosteroids</th>
<th>Progestogens</th>
<th>Prokinetic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>Dexamethasone up to 6mg daily</td>
<td>Megestrol acetate 160mg three times a day</td>
<td>Metoclopramide 10-20mg half an hour before meals</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Anorexia, asthenia</td>
<td>Anorexia, fatigue</td>
<td>Anorexia linked to early satiety or chronic nausea</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>Improves appetite, weakness and can give an improvement in feeling of well-being</td>
<td>Improves appetite, food intake, weight gain, nutritional status, feeling of well-being, fatigue</td>
<td>Improves appetite</td>
</tr>
</tbody>
</table>
| **Risks**   | Wide range of side-effects in long term use:  
  - gastro-intestinal damage  
  - muscle weakness  
  - delirium  
  - osteoporosis  
  - immuno-suppression  
  - glucose intolerance | Usually mild nausea or oedema, but can get thromboembolism | Extrapyramidal effects |
| **Comments** | No change in nutritional status, duration of action may only be 3-4 weeks | Time to improvement of nutritional status is weeks, prolonged duration of action |
Activity 1

1. For what conditions would it be appropriate for a GP to prescribe food supplements to a palliative care patient under the Advisory Committee on Borderline Substances (ACBS) guidelines?

2. What type of foods can be prescribed?
Suggested answers

Activity 1
1. For what conditions would it be appropriate for a GP to prescribe food supplements to a palliative care patient under the ACBS guidelines?

   • dysphagia
   • gastrectomy
   • malnutrition (disease related)
   • nutritional support for adults
   • xerostomia.

2. What type of foods can be prescribed?
   GPs can prescribe any foodstuff on GP10 as long as it is not blacklisted. Some items, while not blacklisted, do not appear on the ACBS list in the British National Formulary. GPs may still prescribe these and pharmacists supply them. The prescribing advisers may however question the GP about the appropriateness of prescribing such items.

Enteral feeding is the delivery of nutrition via a tube into the gastro-intestinal tract. There are many benefits in feeding cancer patients. Ethical issues are identified with regard to commencing or stopping enteral feeding in advanced disease. Cachexia is unlikely to be reversed.

Enteral feeding
There are four main types of tubes for enteral feeding

   • Nasogastric tube (NGT)
   • Percutaneous endoscopic gastrostomy tube (PEG)
   • Radiologically inserted gastrostomy (RIG)
   • Percutaneous endoscopic jejunostomy (PEJ)

In all patients who are unable to take oral medication, there is a need to review medication before considering an alternative formulation, route or medication. When other routes are unsuitable (e.g. rectal), medication may be administered via enteral feeding tubes in patients on enteral nutrition although careful consideration is required. The addition of medicines to the enteral feed is not recommended.

Administration of a medicine via an enteral feeding tube, and crushing tablets or opening capsules to facilitate administration by this route, are almost always unlicensed methods of administration. The prescriber should specifically indicate on the prescription that this route is to be used, and whilst the prescriber is responsible for prescribing outwith license, others involved e.g. pharmacist and person administering, share responsibility for use of medicines in this way.
Pharmacists should be aware of the potential for differences in therapeutic response and/or side effects when medicines intended for oral or parenteral administration are given by the enteral route, and hence the need for careful monitoring. Reasons for this include binding of the medicine to the tube, altered absorption due to interaction with the feed constituents or delivery of the medicine to a different part of the gastro-intestinal tract.

Factors to be considered when administering medicines through an enteral feeding tube:
- choice of formulation
- tube type
- medicine/feed interactions
- site of tube and medicine absorption.

**Choice of formulation**
A thorough review of all medication is appropriate when enteral feeding is commenced. When changing formulations, medicines may require dosage or frequency adjustments e.g. digoxin, phenytoin. Also consider whether there is an alternative formulation of the medicine which can be given via an alternative (and licensed) route, or a different medicine would be more suitable e.g. changing isosorbide mononitrate to a glyceryl trinitrate patch.

Factors to consider when choosing a suitable formulation for administration through an enteral feeding tube include:
- The preferred and easiest way is to use a liquid preparation. However, many liquid preparations are sweetened with sorbitol, which is a laxative and can cause abdominal cramps and diarrhoea when the daily dose is 7.5g or more. Sorbitol containing preparations should be diluted with water immediately before administration. Further dilution may also be required for some other liquids e.g. thick suspensions.
- Dispersible or soluble tablets are preferable to crushing tablets, but the sodium content in dispersible and effervescent tablets may need to be considered.
- It is necessary to consider granule size when administering granular formulations e.g. lanzoprazole Fas Tabs as large granules may block fine bore feeding tubes.
- The health and safety risk of crushing tablets or opening capsules should be considered. Generally, cytotoxics, corticosteroids, hormones, hormone antagonists, antiretrovirals, aspirin, NSAIDs, antibiotics and prostaglandin analogues are not to be crushed.
- Formulations unsuitable for crushing and hence for administration through enteral tubes include:
  - Enteric coated tablets
  - Buccal and sublingual tablets (but the patient may still be able to take these by the buccal or sublingual route)
  - Chewable tablets
  - Modified release preparations (some capsules containing modified release granules can be opened and the contents given through the tube, but others cannot – seek guidance for each specific product).
Techniques for administering medicines via enteral feeding tubes

Nursing staff and patients / carers require assistance with learning appropriate techniques; the companies supplying enteral feeding products often assist with this but additional support from pharmacists is appropriate and often needed to ensure safe and effective medicine administration. The practicalities of measuring and administering complex medication regimes are time consuming and can be burdensome for patients and carers.

There are several resources available detailing suggested techniques for administering medicines through feeding tubes⁵,⁶,⁷, and these can generally be accessed via Medicines Information Pharmacists in hospitals and from Specialist Palliative Care Pharmacists.

Important points are:

- To minimise errors, medicines intended for administration through enteral tubes should be drawn up and administered using an oral medication syringe. These are now designed with a wider tip so that they will not fit into hypodermic needles or ports on IV lines. The National Patient Safety Agency has issued an alert ‘Promoting safer measurement and administration of liquid medicines via oral and other enteral routes’⁸ to reduce the risks of oral medicines being inadvertently administered intravenously.

- To flush the tube with water (e.g. 30ml) before commencing and after medicine administration

- To give each medicine individually and flush the tube with water (e.g. 10ml) between each medicine; it is however useful to have all medicines prepared ready to administer before starting the process

- To consider the potential for interactions between medicines or between a medicine and the feed, which may mean having to give some medicines at a different time

- Use either a 50ml bladder tipped enteral or oral syringe for administration
  - to prevent inadvertent administration by injectable route; there have been fatalities when this has occurred
  - the wider bore of a 50ml syringe is advocated to minimise the risk of rupturing the tube during administration; some practitioners favour removing the syringe plunger and using the barrel as a funnel to deliver the medicines under gravity, and this removes the risk of rupturing the tube and tends to be a simpler process for patients / carers to manage

- Opinions on whether to use tap water, distilled water or sterile water vary; check local guidance. Some medicines react with the ions in tap or bottled water e.g. ciprofloxacin, doxazosin. Cooled freshly boiled water or sterile water from a freshly opened container is recommended for patients who are immunosuppressed⁴. Some units may advise sterile water in jejunostomy feeding.
Tube type
The tube size affects medicine administration. Fine bore enteral feeding tubes are unsuitable for some thick liquids and dispersible tablets.

Occlusion of small bore feeding tubes may occur in up to 15% of patients. Tube blockage may be avoided by:
- using appropriate formulations
- ensuring tablets are fully crushed, if appropriate
- using correct flushing techniques
- avoiding medicine interactions with feeds
- avoiding use of acidic liquids
- consideration of feeding tube size (small bore tubes are more likely to block).

Medicine/feed interactions
Timing of enteral nutrition varies, but in an in-patient setting is often given continuously over 12-24 hours via an infusion pump. Appropriate timing of medication administration in relation to the feed may help minimise medicine-feed interactions and, as with oral medication, may help maximise absorption of medicines. Medicines may interact directly or indirectly with enteral feeds. Medicine interactions with enteral feeds have been reported in the literature. Factors to prompt further clarification of potential interactions include medicines which need to be given on an empty stomach and medicines with a narrow therapeutic index.

Site of tube and medicine absorption
There are more likely to be problems with absorption when the tube is placed beyond the stomach, such as with percutaneous endoscopic jejunostomy (PEJ) tubes. In this case, the use of alternative routes should be considered and an awareness of situations in which the tube may extend beyond the medicine’s main site of absorption is needed. Medicines that may be affected by this include digoxin, cephalexin, ketoconazole, phenytoin and other anticonvulsants.

Summary
When the oral route is not available, alternative routes of administration need to be found. In patients receiving enteral feeding the enteral route is an option. A number of factors need to be considered in order that the medicine is administered successfully. Reference to the literature will help in confirming whether a medicine can be administered enterally. The British Association for Parenteral and Enteral Nutrition have developed information resources on this subject (www.bapen.org.uk see sheet on enteral feeding in particular).
Activity

- You might like to find out whether you can observe administration of medicines in a patient receiving enteral feeding to increase your awareness of the practicalities involved. Consider who you could approach to do this e.g. District Nurse, palliative care pharmacist, care of the elderly ward or ward dealing with patients who have had head and neck surgery, hospice – or you may already know a patient who has their medicines prescribed by this route.

- Establish what guidelines on enteral administration of medicines are in use in your area.
The Patient’s View: Tony and Sue

Sue: “The only advice we can give here is to eat as much as possible. Even for obese patients, dieting is not likely to help once the diagnosis has been made. Healthy eating becomes far less relevant; if ice cream is the only thing you can eat, then eat it. Try full cream milk and butter in mashed potatoes, and tempt them with puddings, soup, alcoholic aperitifs and anything else the patient fancies.”

“Using a small plate may help, as may eating smaller portions more regularly. Homemade ice lollies are worth a try. And be prepared for some interesting food fads: Tony ate two large jars of pickled onions every week. Other previous favourites were useless – he has never managed a pint of beer since!”

Practice Points

Consider the types and flavours of nutritional supplements that are kept within your pharmacy and suggest recipes for incorporating these supplements into meals. If possible, try them out yourself.

References

Chapter 8  Mouth care
Objectives

On completion of this chapter you should be able to:

- list the common oral problems encountered by palliative care patients
- explain the management of common oral problems encountered by palliative care patients
- list the medicines which may exacerbate oral problems in palliative care patients
- describe measures to prevent oral problems in palliative care patients.
Chapter 8
Mouth care

Description of symptom
Oral and dental disease can cause unpleasant and distressing symptoms in patients suffering from advanced disease. Problems may be so severe that they result in a reduction in the intake of fluid and food, contributing to anorexia. It is important to note that many patients do not complain spontaneously of what they believe to be inevitable discomfort in their mouths.

Common oral problems and their management
Good mouth care should be promoted in the palliative care patient and problems anticipated and treated as necessary. The predominant oral problems experienced by patients with advanced disease and aspects of their management are described in Clinical Knowledge Summaries (formerly NHS Prodigy) which may be accessed at the following website www.cks.library.nhs.uk/home and under “Topics” click on “Palliative Care”.

Common oral problems include:
- dry mouth
- painful mouth, causes of which include: ulceration-viral, aphthous, neutropenic
- inflammation due to infections such as oral candidiasis, mucositis
- halitosis
- alteration in taste.

The Patient’s View: Tony and Sue
Sue: “Prevention is so much easier than cure. We bought a soft toothbrush, which was far less likely to cause bleeding gums. A trip to the dentist fairly soon after Tony’s diagnosis sorted out one or two minor fillings, but toothache was a problem during chemotherapy and has been ever since. Lypsyl every hour or so kept sore, cracked lips at bay, and Tony used lots of alcohol free mouthwash (the hospital’s recommendation was Difflam). He also drank lots of liquid and avoided anything too hot, too cold or too spicy. Pineapple (fresh or tinned) was brilliant for dealing with nasty tastes in the mouth.”

“Sore mouths are common in patients who are receiving chemotherapy (it can affect the oral mucosa leaving it open to bacterial or fungal infections). Mouthwashes, particularly those containing chlorhexidine, are useful. (Some patients find that mouthwashes containing alcohol may sting or cause drying to an already inflamed mouth, yet most proprietary mouthwashes have some alcohol in them).”

“Although it is outside their licensed indications, it is sometimes helpful to dilute mouthwashes such as Corsodyl with water. Other patients find that mouthwashes containing hydrogen peroxide, such as Peroxyl, are helpful.”

“Using a soft toothbrush helps. Attention to oral hygiene is essential, including frequent rinsing with water.”
Practice Points
Two products used in the management of oral problems in palliative care are Gelclair sachets and Oxetacaine and antacid liquid. For each product find out:
1. What the indications are for their use
2. How and where they can be obtained in your workplace
3. What counselling a patient may require if they are advised to use either of these products

Now read Section 5 ‘Oral health in patients with advanced disease’ in The ABC of Palliative Care (second edition) included with this pack, and look at the ‘Mouthcare’ section in The Lothian Palliative Care Guidelines at www.palliativecareguidelines.scot.nhs.uk/symptom_control/mouthcare.asp

Summary of articles
- A clean, comfortable and healthy mouth is a requirement for optimal palliative care.
- Palliative care patients should be specifically questioned about mouth problems and their mouth examined regularly to reveal signs of treatable oral problems.
- Regular oral hygiene, at least twice daily and more frequently when necessary, is essential for all palliative care patients.
- Encourage the intake of oral fluids to maintain good hydration.
- Common oral problems include infection, dry mouth, dirty mouth, painful mouth.
- Treatable causes of dry mouth include candidiasis, antimuscarinic drugs, anxiety and dehydration.
- Some products, marketed (and promoted) for dry mouth, are not licensed as medicines and cannot be prescribed on the NHS.
- Severe pain due to mucositis occasionally needs systemic analgesics such as opioids, with the dose titrated against the pain. Oramorph unit dose vials - which were alcohol free and could be used as a mouthwash prior to swallowing - are no longer available. The only alcohol free opioid solution currently available is OxyNorm Liquid.
- Risk factors for oral problems in palliative care patients include: debility, dry mouth, chemotherapy, local irradiation, dehydration.
Activity 1

Mr F is a 77 year old patient with lung cancer. He has just completed a course of chemotherapy. He lives with his wife at home but is finding it difficult to manage. He complains that his appetite is poor as he is finding that food tastes strange and is sometimes difficult to swallow. He has just completed a course of amoxicillin for a chest infection. His current medication is as follows:

- Morphine sulphate immediate release liquid 2mg four times daily and as required for breathlessness
- Salbutamol Easibreathe inhaler two puffs as required for breathlessness
- Beclomethasone 100 Easibreathe inhaler two puffs twice daily
- Dexamethasone 6mg daily (reducing course)
- Isosorbide mononitrate modified release 60mg daily
- GTN tablets 500mcg if required for chest pain
- Co-danthramer 10ml twice daily
- Glycerin and lemon mouthwash twice daily

Mr F’s tongue is red with white plaques on the tongue and the back of the throat.

A clinical diagnosis of oral candidiasis is confirmed by swab.

1. What risk factors does Mr F have for a mouth infection?
2. What are the treatment options for Mr F?

3. What advice would you give Mr F to avoid further episodes of oral candidiasis?
Suggested answers

Activity 1

1. What risk factors does Mr F have for a mouth infection?

Risk factors for the development of an infected mouth include:

- immunocompromised following cytotoxic chemotherapy
- recent antibiotic use
- dry mouth due to morphine
- dry mouth due to lemon and glycerin mouthwash
- use of inhaled and oral corticosteroids.

2. What are the treatment options for Mr F?

The treatment options for oral candidiasis include:

Non-specific measures

Good oral hygiene and ensuring that denture wearers remove their prostheses overnight and soak them in a suitable cleansing solution, and brush them thoroughly.

Use water or saline for rinsing.

Specific measures

Antifungal treatment may be provided topically or systemically.

Topical treatments:

- are mainly nystatin and amphotericin B, neither of which is absorbed systemically.
- can be difficult to use and patients may dislike the taste.
- may be ineffective because of failure to hold the liquid formulation in the mouth for a sufficient time.
- should be used after meals and mouthcare (i.e. teeth cleaning). Encourage the patient to wait 30 minutes before drinking or eating after administration of treatment. Continue with treatment for two days after resolution of symptoms.
- require the patient to remove dentures and soak in denture cleaning solution overnight, then rinse and clean before replacing. Avoid the concurrent use of chlorhexidine mouthwash with nystatin.

If angular cheilitis is present consider miconazole oral gel. Although topical, systemic absorption can occur and thus medicine interactions.

Systemic treatments

Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred. Fluconazole is the drug of choice being very well absorbed after oral administration. A liquid formulation is also available and may be used as a mouthwash prior to swallowing. Dose:- 50-100mg daily for 7-14 days. Note medicine interactions.
3. What advice would you give Mr F to avoid further episodes of oral candidiasis?

- **Try to maintain good regular oral hygiene.**
- **Maintain a good fluid intake with regular sips of water or crushed ice-cubes.**
- **Substitute easibreathe inhaler for an mdI plus spacer and rinse mouth well with water after using steroid inhaler.**
- **Substitute GTN tablets for a spray.**
- **Glycerin can produce a drying effect in the mouth and is best avoided. Lemon juice exhausts salivary secretion. Replace glycerin and lemon mouthwash with a saliva substitute. The choice should be based on any local prescribing guideline and patient preference. Avoid Glandosane spray in a patient with their own teeth as it is acidic.**

References


Additional References

Chapter 9 Wound and Skin Care/Lymphoedema
Objectives

On completion of this chapter you should be able to:

- list the common skin problems encountered by palliative care patients
- explain the management of common skin problems encountered by palliative care patients
- describe measures to prevent skin problems in palliative care patients.
Wounds
The same basic principles apply to wound care within the palliative care setting as to any other setting, although in patients with advanced illness, the goals of care may shift from healing to comfort and palliation. As with other aspects of palliative care, optimal management requires comprehensive assessment.

Adapted from Top ten tips for assessing and treating difficult wounds – Diane Laverty, Royal Free Hospital, London1.

1. Assess wound – size, shape, location, symptoms – identify those most troublesome to the patient (bleeding, malodour, exudates, infection, pain, pruritis), surrounding skin condition
2. History – previous dressings, topicals and methods used and the outcome
3. Accurate documentation – each wound is unique
4. Be clear about aims of care – treat the whole patient not just the wound, be realistic, acknowledge issues of body image and vulnerability
5. Choose appropriate dressing products i.e. purpose, properties and manner of action and involve patient in care.

Fungating wounds
Fungating wounds are caused by infiltration and proliferation of malignant cells within the skin, either from a primary tumour or metastases. Such wounds rarely heal, and the aim is to promote patient comfort and quality of life. They may cause psychological distress and disrupt social life due to altered body image. Commonest sites are breast and head and neck. Palliative interventions such as radiotherapy may sometimes be used.

Fungating wounds are commonly associated with:
• Malodour - local guidelines should be available regarding use of metronidazole systemically or topically if anaerobic contamination is suspected. Essential oils, used under the supervision of a specialist may be recommended.
• Exudate – finding a suitable dressing to stay in place and control exudate can be challenging; it is important to check that dressings selected are included in the Drug Tariff and can hence be prescribed. For wounds with a huge exudate, protection of the surrounding skin is important to prevent maceration.

• Pain – if pain is exacerbated by dressing change, ensure an appropriate dressing is used to minimise frequency of change and further damage to fragile tissue; consider giving a short acting opioid in advance of the procedure

• Bleeding – medicines licensed for other indications or routes may occasionally be used topically when persistent bleeding is troublesome; specialist advice should be sought

Topical Opioids

From UKMi Q&As available at www.Tiny.cc/WTrYa

Pain associated with skin ulcers of benign or malignant origin is a common problem in palliative care, occurring in about 26% of hospice patients. Such pain is often unresponsive to systemic analgesics. Traditionally, it has been thought that opioids only have a central effect therefore topical administration would be ineffective locally. However, more recently it is suggested that peripheral opioid receptors become activated by injury allowing topical application to be an effective route of administration for opioids. The topical route has the advantage of few side effects as systemic bioavailability is negligible. This Medicines Q&A reviews the evidence for efficacy of topical opioids in the management of painful skin ulcers and discusses some practical aspects of therapy. Used as an adjunct to systemic analgesia, reduction or cessation of concomitant analgesics may be possible. The most commonly used topical formulation is morphine sulphate in ‘Intrasite’ gel.

A recent systematic review concluded that there is support for the use of topical opioids, but further studies are required to determine the most effective opioid, dose, administration schedule, carrier and the types of wounds suitable for treatment in this way.

Practice Points

Find out if topical opioids are used in your local area, which preparations and from where are they accessed.
Skin Care

Preventing problems occurring is usually far easier than treating skin which has become damaged. Pharmacy staff are ideally placed to provide advice on basic skin care to patients and carers (and the latter often find this is an area of care where they can assist, and feel they are contributing something useful) and additional considerations are identified below.

Chemotherapy can cause dry, sensitive skin and may cause brittle nails. This may be aggravated in harsh environments such as chlorinated swimming pool water. The use of regular bland moisturisers is especially helpful to avoid dehydration and minimise itching. Patients should advise their doctor if rashes appear as this may be medicine related e.g. fluorouracil or capecitabine. The risk of cuts is greater with wet shaving than with electric razors and so may be best avoided.

Some chemotherapy leads to photosensitivity and ensuring sun protection i.e. avoidance, covering up with natural fibres, wearing head protection and high factor sunscreen is essential.

Hair loss may cause distress to patients and families. Practical advice and reassurance may be required. A list of good wig supplier addresses may be helpful.

Radiotherapy may cause the development of a reaction similar to sunburn. This often occurs a few weeks after treatment and may become sore and itchy. Skin may remain sensitive to sun exposure and should have additional protection for at least a year. Patients may be asked to avoid washing the area, using cool water, not to soak too long and to pat dry and avoid using drying agents such as talcs, soaps, deodorant or perfumes. Care of the skin should be advised by specialist staff. Advice as regards swimming and shaving following chemotherapy is equally relevant here.

Pruritis (itch) may be caused by dry, irritable skin, skin infections (occasionally nail infections), some medicines e.g. morphine, jaundice or the condition itself e.g. lymphomas. Where possible identify the underlying cause and treat appropriately.

The Patient’s View: Tony and Sue

Tony: “My hair started falling out in large handfuls several weeks after the first chemotherapy treatment. It was a fairly easy decision to have it all shaved off immediately but very difficult to come to terms with the new look. However, several months later I started to look on it in a positive way – the treatment was definitely having one of its predicted effects, and hopefully it was working equally well on the cancer! A good selection of hats proved useful both in hot and cold weather and sunscreen was very necessary. I soon learned how many hard objects there are within range of an exposed scalp!”
Practice Points
‘Look Good….feel Better’ is a programme run by some hospitals and support groups that gives expert advice on make-up and skin care. It also has a website which deals with general skin problems during cancer treatment as well as hair loss, wigs and hints on how to make the best of your appearance (which in itself can provide a psychological boost to some patients). It is well worth signposting patients to [www.lookgoodfeelbetter.org](http://www.lookgoodfeelbetter.org).

There is no specific article to read for this chapter. It may be helpful to refer to the most recent BNF chapter 13, Palliative Care Formulary 3rd edition (PCF3) chapter 12 and Oxford Handbook of Palliative Care 2nd edition chapter 6f. Refer also to local formularies and local Tissue Viability specialists’ guidelines.

**Lymphoedema**

Lymphoedema occurs when drainage routes through the lymphatic system become blocked (e.g. cancer) or damaged (e.g. surgery) resulting in accumulation of lymph in the tissues and hence swelling, most often in the arms or legs but occasionally in other parts of the body e.g. trunk, groin or face. Changes in the tissues can occur e.g. fibrosis leading to an increased risk of infection.

There is no permanent cure for lymphoedema. But it is possible to control it with treatment to reduce swelling and prevent more fluid from building up.

There are five main types of treatment:

- care of the skin to prevent damage and infection
- compression of the limb with elastic sleeves or stockings, or bandaging
- exercise to help the lymph flow
- positioning of the limb and regular movement to use gravity and muscle movement to drain fluid
- massage to help disperse fluid that has built up.


Practice Points
What information would you include in a patient information leaflet about the management of lymphoedema?
References
1 Laverty D Top ten tips for assessing and treating difficult wounds. Progress in Palliative Care 2008;16(1):3
2 NHS UKMi Medicines Q&As No. 79.1 (January 2009) ‘Are topical opioids useful in the management of skin ulcers in palliative care patients?’

Additional References
- Best Practice Statement “Prevention and Management of Pressure Ulcers” NHS Quality Improvement Scotland Edinburgh March 2009 www.nhshealthquality.org
Chapter 10 Neurological complications in palliative care
Objectives

On completion of this chapter you should be able to:

- list the common signs of neurological complications exhibited by palliative care patients
- list the common side-effects of the different classes of medicines used for neurological complications in palliative care patients
- identify problems associated with abruptly stopping antidepressants
- identify ‘serotonergic syndrome’ and advise on its management in the palliative care patient.
Chapter 10

Neurological complications in palliative care

Depression

Description of symptoms

It is estimated that 25% of the population develop a significant mood disorder in advanced cancer. Depression in palliative care patients may be underdiagnosed although this should not be confused with appropriate sadness at the end of life.

Common signs of depression are depressed mood, loss of interest and enjoyment, decreased concentration and attention, decreased self confidence and feelings of guilt. Some other signs of depression which may be masked by symptoms related to terminal illness are decreased energy levels, increased tiredness, bleak outlook regarding the future, disturbed sleep, decreased appetite and weight loss.

Risk factors for anxiety and depression are:

- pre-existing psychiatric disorders
- poorly controlled symptoms
- poor relationships with staff and with family/friends
- past medical history of drug and/or alcohol misuse
- concurrent adverse social history
- lack of family/friend support.
### Treatment of depression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants (TCA) e.g. amitriptyline</td>
<td>Sedative, anxiolytic</td>
<td>Anticholinergic side effects including dry mouth.</td>
<td>Anticholinergic side effects may exacerbate dry mouth caused by opioids. Patient may be prescribed amitriptyline low dose for neuropathic pain.</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRI) e.g. citalopram, fluoxetine</td>
<td>Few anticholinergic effects, safer in overdose, non sedative</td>
<td>Nausea, vomiting, diarrhoea, anxiety, may increase risk of GI bleed</td>
<td></td>
</tr>
<tr>
<td>Noradrenergic and specific serotonin inhibitor e.g. mirtazapine</td>
<td>Few anticholinergic effects, useful if agitation/anxiety</td>
<td>Can cause sedation initially</td>
<td></td>
</tr>
<tr>
<td>Serotonin and noradrenaline reuptake inhibitor e.g. venlafaxine</td>
<td>START ONLY UNDER SPECIALIST ADVICE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Now read Section 9 ‘Depression, anxiety and confusion’ in *The ABC of Palliative Care (second edition)* included with this pack. Also read the following on depression in the terminally ill from the *European Journal of Palliative Care*. 

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Diagnosing and treating depression in the terminally ill

Depressive illness is common but difficult to detect in cancer patients. Patricia Casey explains how to differentiate possible manifestations of depression.

The word ‘depression’ has many meanings and nowhere is the clinical dilemma that it poses more apparent than in patients with serious and terminal physical illness. Depression may mean boredom or describe a state of transient gloom – such as when a patient first goes to hospital and is separated from family and friends. It might imply a more persistent feeling of unremitting sadness, directly related to the ongoing illness. Finally, it may be used to describe long-standing symptoms with their own momentum, irrespective of the severity or nature of the physical illness. This is called depressive illness.

The reported prevalence of depressive illness among cancer patients varies from 4.5–77%. This wide variation is due to the absence of reliable diagnostic criteria and the use of a variety of screening instruments. In considering the management of depression, it is first essential to examine the issue of diagnosis and how this is made in the context of palliative care.

Definitions of depression

- **Depressive illness** is a disorder in which sadness and gloom are the dominant symptoms. Some patients describe anxiety rather than depression as the principal symptom and in depressive illness both anxiety and depression invariably co-exist as symptoms. This mixture frequently leads to the misdiagnosis of depressive illness as an anxiety state and consequently to inappropriate treatment. The depressed feeling is unremitting and largely unresponsive to social or environmental change. Feelings of happiness and...
pleasure in seeing a relative, if present at all, are brief. The presence of a major stressor such as a life-threatening illness may also lead to misdiagnosis, with comments such as, ‘isn’t it natural to feel like that when you are so ill?’ Such statements are based on the view that the symptoms are understandable in the context, making the distinction between reasonable sadness and depressive illness so difficult. However, this distinction is extremely important in patients receiving palliative care.

- The term ‘reactive depression’ is no longer used in modern psychiatry because of confusion associated with its meaning. For some clinicians it described a depressive illness with a precipitant, while for others it was an understandable but exaggerated reaction to an event that did not respond to or require antidepresants. The abnormal reaction was believed to be rooted in the personality of the individual, who had poor personal and emotional resources.

- The first definition is now subsumed under the rubric of depressive illness, while the latter belongs to the category known as adjustment disorders. This distinction is at the nub of depressive symptomatology in those receiving palliative care. There are two clusters of depressive symptoms that the clinician must treat – adjustment reactions and depressive illness. The distinction is clinically difficult to detect but important.

**Antidepressants**

The clinical use of antidepressants must be guided by their effectiveness in the particular disorder. Those with a depressive illness respond well to such treatments and the improvement in symptoms contributes to a reduction in the distress associated with life-threatening illness; they also facilitate engagement with psychotherapy. To offer those with depressive illness counselling alone is to withhold an effective intervention, since talking and listening alone have not been shown to be effective in treating depressive disorders.

On the other hand, to give antidepressants to those suffering from an adjustment reaction rather than a depressive illness imposes a medical model on a disorder outside this framework. For such patients, psychotherapy is an effective intervention and the use of antidepressants will not help in symptom reduction (with the exception of sleep impairment).

**Key symptoms**

Many of the symptoms associated with depressive illness in the general population are unhelpful when making the diagnosis in a palliative care setting, since they are associated with the physical illness itself and with inactivity. Included in this category are:

- Appetite reduction.
- Constipation.
- Weight loss.
- Lethargy.

Moreover, some symptoms, features of both depressive illness and adjustment disorders, are unhelpful in determining the diagnosis. Included in this group are sadness, tearfulness, loss of hope, sleep disturbance (particular difficulty in initiating sleep) and poor concentration.

Other symptoms, prominent in depressive illness, may be a pointer to that diagnosis. These include:

- Early morning waking.
- Diurnal mood change, with mood being worse in the early morning or at night.
- Feelings of being a burden when this is manifestly not based on reality.
- Pathological guilt.

Active suicidal ideation (‘I want to die; I have thought about harming myself’) must be distinguished from passive death wishes (‘I wish I could go to sleep and not wake up; I have never thought of harming myself’) since the former is invariably a feature of depressive illness.

Suicidal behaviour is rarely seen in cancer patients except in the context of untreated underlying depressive illness. Anxiety symptoms – especially physical ones such as palpitations, sweating, dizziness, breathing difficulty and panic attacks – are more indicative of depressive illness and may feature less prominently in adjustment disorders. Delusions and hallucinations, although rare, indicate severe depressive illness (depressive psychosis).

**Other diagnostic features**

As well as the symptom pattern, a number of other features may assist in making a diagnosis. In particular, a change from the usual symptoms or functioning may herald a depres-

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**Key points**

- Depressive symptoms are very common in the terminally ill.

- Depressive illness is common throughout the general population, although accurate figures for its prevalence are not available.

- Antidepressants, along with psychotherapeutic techniques, have a significant part to play in treating depressive illness, although the former are unlikely to be effective in patients with adjustment disorders, who probably constitute the largest diagnostic group in this setting.
Psychological issues

Failure in efforts to comfort the patient and a lack of response to counselling should alert the clinician to the possibility of depressive illness.

Not surprisingly, most patients with cancer exhibit some emotional symptoms but a worsening of these, in the absence of any explicable physical change, is significant.

The patient who hitherto seemed to have adjusted to being seriously ill will suddenly and inexplicably become tearful and distressed or may experience panic attacks for the first time. Failure in efforts to comfort the patient emotionally and, especially, a lack of response to counselling over several sessions should alert the clinician to the possibility of depressive illness rather than adjustment disorder.

A past history or a family history of depressive illness should also alert one to this diagnosis. The previous coping strategies of the patient are likely to assist further in clarifying the diagnosis. The patient who always reacted badly to stress and required input from professionals is likely to react adversely when seriously physically ill.

Questionnaires

It is often assumed that using instruments such as the Hospital Anxiety and Depression Scale (HADS) will confirm the diagnosis, especially since this instrument was designed with physical illness in mind. However, this is not a diagnostic scale but rather a general measure of symptomatology and, while it can be used as a severity and change measure, it will not discriminate between adjustment disorder and depressive illness.

Differential diagnoses: anxiety states

The presence of anxiety symptoms may lead the unwary to an incorrect diagnosis of panic disorder or generalised anxiety. The age of the patient is helpful here, since first-time anxiety states are uncommon in the over-40s. A further key to making the diagnosis is the presence of other depressive-type symptoms, which may be largely obscured by the anxiety. These include concentration problems, which are not common in anxiety states, tearfulness (often ascribed by the patient to being fed up with the symptoms) and a diurnal swing to anxiety and panic.

Psychological treatments

All gloomy and sad people benefit from psychological support. For patients meeting the criteria for adjustment disorders, this may be all that is required. They are assisted in ‘working through’ their feelings to a state of adjustment and acceptance. ‘Counselling’ is the term used to describe the form of non-directive therapy developed by Carl Rogers, in which listening as well as talking are used therapeutically. The aim is to make the concealed fears and emotions related to the illness and to dying explicit.

Although much has been written about counselling, there have been few formal studies examining its efficacy and one recent study failed to find any benefit in counselling general practice patients when compared with routine management for such emotional disorders. Moreover, there have been no studies of its effectiveness in the palliative care setting in spite of being the cornerstone of management for depressive symptoms for many years.

Cognitive therapy is a more structured treatment that has been shown to be effective, if time-consuming, in depressive illness. It is not used generally in palliative care due to the lengthy period required for improvement.
Equally, psychodynamic psychotherapy is not useful in this population, as it is more time-intensive than cognitive therapy and has not been shown to be efficacious in depressive symptoms or disorders.

However, while appreciating professional support and concern, and the opportunity to talk, those with a depressive illness are unlikely to experience any demonstrable reduction in emotional symptomatology without the concurrent use of antidepressants.

**Pharmacotherapy**

Antidepressants are essential to symptomatic improvement in depressive illness. However, those with adjustment disorders do not benefit and may even feel worse, because of side-effects. These drugs do not cause dependence. Antidepressants are divided into several groups (Table 1):

- **Tricyclic antidepressants** (TCAs) are the oldest. The pattern of side-effects, such as cardiac arrhythmias and postural hypotension, may preclude their use in those with heart disease. Some patients feel drowsy when taking TCAs, although this side-effect can be used beneficially in those with insomnia, obviating the need for hypnotics. Those with anxiety symptoms also report a reduction in symptoms after a few days, although the effect on mood takes over two weeks to develop. Moreover, some drugs, in particular amitriptyline and dothiepin, have an adjunctive role in analgesia. Patients with suicidal thoughts and plans should not be given these drugs, as they can be fatal in overdose.

- **Specific serotonin re-uptake inhibitors** (SSRIs) have received a lot of public attention, largely due to their safety in overdose. They are as effective as the TCAs and the speed of onset of action is similar. However, their profile of side-effects is different: gastrointestinal disturbance is particularly common and their lack of sedative effect requires that a hypnotic be given initially when insomnia is present, although this can be discontinued when the mood-elevating effect develops. At that stage, sleep will also improve.

- **Mono-amine oxidase inhibitors** (MAOIs) are less commonly used due to the dietary restrictions imposed by their use.

- **Lithium** augmentation, in combination with either the TCAs or the SSRIs, is a strategy used in refractory depression (resistant). Although electroconvulsive therapy is an excellent treatment, it is reserved for severe depressive illness, usually with delusions.

**Psychostimulants** also have limited success in patients with refractory depressive illness.

**Benzodiazepine tranquillisers** and hypnotics may be useful in the short term for insomnia and for transient anxiety. When used in conjunction with SSRIs, they can be discontinued when the antidepressant effect develops. In combination with TCAs, they may lead to excessive drowsiness. A comprehensive review of the pharmacotherapy of emotional disorders in palliative care is available elsewhere.

The role of **newer antidepressants** such as serotonin and non-adrenergic re-uptake inhibitors (SNRIs) in patients with refractory depression remains untested.

**Conclusion**

Depressive symptoms are very common among patients seen in a palliative care setting. Depressive illness is also common, although accurate figures for its prevalence are not available. Antidepressants, along with psychotherapeutic techniques, have a significant part to play in treating depressive illness. However, the former are unlikely to be effective in patients with adjustment disorder who probably constitute the largest diagnostic group in this setting.

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**Table 1. Examples of different types of antidepressants in common use**

<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic TCAs</td>
<td>Dothiepin, amitriptyline, lofepramine</td>
</tr>
<tr>
<td>Specific serotonin re-uptake inhibitors (SSRIs)</td>
<td>Fluoxetine, paroxetine, sertraline</td>
</tr>
<tr>
<td>Mono-amine oxidase inhibitors (MAOIs)</td>
<td>Phenelzine, tranylcyromine, moclobemide</td>
</tr>
<tr>
<td>Newer compounds</td>
<td>Nefazodone, mirtazapine, reboxetine</td>
</tr>
</tbody>
</table>

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**References**


**Patricia Casey, Professor in Psychiatry, Department of Adult Psychiatry, Mater Hospital, University College Dublin, Dublin, Ireland**
Summary of article

- It is important to differentiate between appropriate sadness at the end of life and clinical depression.
- Identify any modifiable risk factors.
- Treat depression promptly if appropriate.
- Treat/address any reversible causes.
- Ensure the addition of any antidepressants will not worsen side effects of other medication.

Delirium and confusion

Delirium

Delirium is an acute confusional state which is commonly seen in hospitalised terminally ill patients. It is important to differentiate delirium from dementia, a condition which primarily affects cognition. The prevalence rates of delirium in advanced cancer patients admitted to an acute hospital or hospice are approximately 28-48% with as many as 85-90% experiencing delirium in the hours or days before death\(^1,2\). The mechanisms of delirium are poorly understood, however, it is thought to be due to decreased anticholinergic activity and an increase in dopaminergic activity. A deficiency in thiamine, hypoxia and hypoglycaemia all cause a reduction in anticholinergic activity. This may explain partly why antidopaminergic drugs such as haloperidol can improve symptoms.

Assessment is the key to treating delirium effectively as it is often misdiagnosed as depression or dementia. There are 3 subtypes of delirium, hyperactive, hypoactive and mixed.

Reversible causes of delirium and confusion include:

- Hypercalcaemia
- Drug induced (opioids, steroids, alcohol withdrawal, benzodiazepines, benzodiazepine withdrawal, SSRI withdrawal, nicotine withdrawal, digoxin and lithium)
- Hyponatraemia
- Transient Ischaemic Attack (TIA)
- Thiamine (vitamin B1 deficiency)
- Renal failure
- Anxiety/depression.
- Non-convulsive status epilepticus
- Liver Failure
- Infection
- Cerebral tumour
- Cerebral tumour
- Disorientation – change of environment

Treatment should be by treating the reversible cause. Drug treatment should only be instituted if necessary. Haloperidol and other antipsychotics can be of use but patients should be monitored for any signs of extrapyramidal reactions.
Confusion
The threshold for confusion is lowered in cachectic and anxious patients and therefore it is important to make the treatment environment as stable, safe and comfortable as possible.

Treatment options:
- Haloperidol - indications are drug toxicity, altered sensorium, metabolic upsets and hallucinations.
- Diazepam (oral only) - indications are anxiety and distress
- Midazolam - indications are anxiety, distress and risk of seizure
- Levomepromazine (Nozinan) - can be used if there is a need for an alternative or additional sedation.

Seizures in palliative care
Common causes of seizures in palliative care include:
- brain tumour (primary tumour or metastatic site)
- biochemical disturbance (hyponatraemia, SIADH)
- previous cerebrovascular accident
- long standing epilepsy.

The seizures should be classified in accordance with the guidance set out in SIGN 70 - Diagnosis and management of epilepsy in adult patients. SIGN 70 classifies seizures as partial, generalised and unclassified www.sign.ac.uk

Type of seizure
Isolated tonic-clonic seizures sometimes last no more than a few minutes and treatment is not always necessary but may be of benefit if the seizures are causing the patient distress. Grandmal seizures (generalised) and status epilepticus should be treated promptly with midazolam or another benzodiazepine such as lorazepam, diazepam or clonazepam.

Common causes of seizures in terminally ill patients
- **Raised intracranial pressure**
  Intracranial tumours or raised intracranial pressure causing seizures should be treated with dexamethasone at a dose of 8mg twice daily.
- **Biochemical abnormalities**
  Biochemical abnormalities such as hyponatraemia can be as a result of SIADH (syndrome of inappropriate ADH secretion). This can be secondary to drug therapy or due to the ectopic production of ADH from tumours. Seizures can result if the plasma sodium falls below 120mmol/l. Treatment is with fluid restriction, chemotherapy of the tumour or demeclocycline.
- **Alcohol withdrawal**
  Consider alcohol withdrawal as cause and treat if necessary with regular benzodiazepines as per local protocols.
Initiating anticonvulsants
It is appropriate to commence anticonvulsants in palliative care patients experiencing seizures. Valproate is considered the first line treatment for focal and partial seizures and seizures due to intracranial tumours. Carbemazepine and phenytoin are suitable alternatives. If patients are nil by mouth or unable to take medications orally suitable treatments are:
- phenobarbitol by CSCI or daily SC injection
- midazolam by CSCI (can be sedative and unlicensed use)
- clonazepam by CSCI
- carbamazepine and valproate suppositories (caution in bioinequivalence)

Midazolam buccal liquid may be considered for the management of seizures (unlicensed preparation).

Fatigue
Cancer related fatigue is defined by the National Comprehensive Cancer Network as “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning”. Cancer related fatigue is possibly the most important untreated symptom of cancer, is rarely discussed and very often goes untreated. Symptoms include:
- low energy levels
- poor concentration
- confusion
- reduced mobility, independence and self esteem.

Some causes of fatigue are reversible such as opioid induced, anaemia, infection, depression or metabolic causes.

There are different ways to treat fatigue including:
- planning activities to reduce boredom
- energy conservation to prioritise activities
- emotional support
- nutritional support (dexamethasone low dose or megestrol acetate considered)
- practical support including discussion of expectations, with multidisciplinary teams and social work input

Now read about Anxiety and confusion in Section 9 and Fatigue in Section 6 of *The ABC of Palliative Care (second edition)* included with this pack.
Activity 1

Mr S is a 64 year old man with lung cancer and liver and brain metastases. His medicines on admission are:

- Dexamethasone 2mg morning and night
- Amitriptyline 10mg at night
- Morphine sulphate (MST) 20mg twice daily
- Morphine sulphate (Sevredol) 5mg as required
- Senna 2 tablets at night
- Lactulose 10ml twice daily

He complains of feeling anxious, difficulty sleeping and of having a low mood.

1. Comment on Mr S’s medication on admission

2. Consider causes of depression and agitation and suggest non pharmacological treatments

3. Consider pharmacological treatments for depression and agitation
### Activity 2
Complete the blanks in the following table of pharmaceutical care issues

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed medication history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribing of dexamethasone at bedtime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline being taken on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensure appropriate selection of antidepressant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient counselling on new therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Suggested answers

Activity 1

1. Comment on Mr S’s medication on admission
   Question dexamethasone at night. Rationalise to 4mg once daily or 2mg morning and lunchtime (tends to cause insomnia if taken later in the day).
   Check amitriptyline indication - neuropathic pain dose.

2. Consider causes of depression and agitation and suggest non pharmacological treatments
   Check with patient if anything is worrying him. Quite often patients worry about how their families are coping with the diagnosis. Encourage the patient to talk to family. Check if financial assistance required? Do you know who you should refer him to for this?
   Encourage participation in any activities especially those which the patient has enjoyed previously if fit enough. Consider a diary to document what triggers anxiety. Ensure optimal lighting and reassurance.

3. Consider pharmacological treatments for depression and agitation
   Depression - SSRI first line.
   Caution with concomitant amitriptyline.
   Caution with high dose tricyclic and SSRI but generally tolerated with low dose TCA.
## Activity 2

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed medication history</td>
<td>Obtain medication history from patient, family, GP community chemist</td>
<td>Ensure all previous medications which have been tried are known</td>
</tr>
<tr>
<td>Prescribing of dexamethasone at bedtime</td>
<td>Check with patient what time second dose of dexamethasone is taken</td>
<td>Dexamethasone taken at bedtime will cause sleep disturbance</td>
</tr>
<tr>
<td>Amitriptyline being taken on admission</td>
<td>Check indication 10mg is an appropriate dose for neuropathic pain but if this has been started as an antidepressant then the dose should be escalated to therapeutic levels</td>
<td>Ensure that indication for all medicines is known and that the dose is optimised</td>
</tr>
<tr>
<td>Ensure appropriate selection of antidepressant</td>
<td>SSRI first line e.g. citalopram</td>
<td>Ensure appropriate therapy</td>
</tr>
<tr>
<td>Patient counselling on new therapy</td>
<td>Counsel patient and family on abrupt discontinuation of antidepressants, ensure that the patient is aware of length of time taken for therapy to begin to work</td>
<td>Ensure patient expectation are realistic and that withdrawal side effects are minimised</td>
</tr>
</tbody>
</table>
References:


Chapter 11 Last days of life
Objectives

On completion of this chapter you should be able to:

- list the symptoms most common in the last 48 hours of life
- outline which medicines are appropriate to continue and which are not
- explain the possible causes of terminal agitation/restlessness
- outline the management for terminal agitation/restlessness.
Chapter 11
Last days of life

Symptom management
It has been shown that it is almost impossible to accurately predict when patients are going to die even when they have existing advanced, progressive disease\(^1\). Patients can decline gradually over a period of weeks or months, or their condition can progress rapidly over hours or days. This makes the management of this stage of progressive disease difficult; however it is possible to anticipate some of the potential problems. This requires regular review of the patient’s condition and carers’ situation and services must be flexible enough to meet these needs whether they arise gradually or suddenly. Interventions and test requests, including blood tests, need to be assessed as to whether the results will significantly contribute to the way the patient will be treated. If the answer is that they will not, then the tests should not be carried out.

As disease progresses to the last few days, symptoms previously identified persist and new symptoms may arise. The most common symptoms are anorexia, dry mouth, confusion, constipation, dyspnoea, dysphagia, anxiety and pain; all being found in more than 30% of patients with cancer. Similar symptoms are experienced in patients with non-malignant disease\(^2\). Treatment of existing symptoms should always be continued and modified according to response whilst prompt treatment of new symptoms should be initiated.
Agitation

Agitation and confusion are common symptoms during the last few days of life. Common causes and appropriate treatments of agitation are outlined in the table overleaf.

<table>
<thead>
<tr>
<th>Underlying causes of agitation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Looking for reassurance/company</td>
<td>Constant attention and reassurance, verbal communication, physical contact</td>
</tr>
<tr>
<td>Anxiety/anguish</td>
<td>Reassurance, company, familiar surroundings, sedation with midazolam if all else fails</td>
</tr>
<tr>
<td>Distended bladder</td>
<td>Catheterise</td>
</tr>
<tr>
<td>Constipation</td>
<td>Rectal laxatives</td>
</tr>
<tr>
<td>Pressure sore</td>
<td>Avoid unnecessary dressing changes. Increase background pain control. Use local anaesthetic to numb if severe</td>
</tr>
<tr>
<td>Drug withdrawal, e.g. SSRIs, nicotine, opioid, benzodiazepines, alcohol</td>
<td>Restart drug if appropriate or use e.g. nicotine replacement therapy. If not, monitor and sedate if necessary with midazolam</td>
</tr>
<tr>
<td>Pain</td>
<td>Increase analgesia</td>
</tr>
<tr>
<td>Opioid toxicity – suspect if on morphine/diamorphine and renal function reduces or if dose is increased rapidly</td>
<td>Reduce opioid dose, give haloperidol and commence parenteral (subcutaneous) fluids if signs of dehydration are present and this will assist symptom management</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>Positioning, increase/initiate opioid and/or benzodiazepine</td>
</tr>
<tr>
<td>Cerebral anoxia</td>
<td>Sedation with midazolam</td>
</tr>
<tr>
<td>Delirium</td>
<td>Haloperidol, Levomepromazine or sedation with midazolam</td>
</tr>
</tbody>
</table>

The choice of new treatments, and whether to continue existing treatments, needs to be based on the short term goals of maintaining comfort and not intruding on the patients’ or carers’ ability to be together. Parenteral hydration is very controversial. Guidance from national groups¹ has not stilled the debate and a lack of good evidence supporting or refuting the use of hydration in the terminal stages makes the decision to use such treatment difficult. Evidence at present suggests that hydration in imminently dying patients influences neither survival nor symptom control. Thirst can often be caused by medication. It is unlikely that hydration will alleviate this. Instead patients should have good mouth care and their medication reviewed. If hydration is provided then appropriate equipment and monitoring must be available.
Catastrophic Haemorrhage
This is an uncommon but very distressing terminal event for patients, carers and healthcare professionals. Significant bleeding may result from tumour or invasion of blood vessels or bleeding from oesophageal varices. It is important to plan ahead and have agreed a management plan with the patient and/or family. Advance prescribing of e.g. opioid and sedation needs to be in place, usually midazolam intramuscularly or intravenously as the subcutaneous route is not appropriate, which can be repeated as required. It is helpful to have dark coloured towels available to disguise blood loss.

Terminal Agitation
A diagnosis of terminal agitation assumes that reversible conditions are excluded or failing to respond to treatment. Sedation is needed in many patients, but pain (especially from urinary retention) should be excluded or treated appropriately. Part of the assessment should identify who is being adversely affected: the patient, the family and/or the healthcare professionals. Treatment includes keeping the patient’s room quiet and well lit, giving calm reassurance and explanation, minimising disturbances, such as unfamiliar staff, having a trusted family member or friend present and developing a daily routine.

The clinical features initially include restlessness with periods of disorientation (not knowing time, place or people) and also reduced short term memory. Acute confusion usually fluctuates with periods of normality interspersed between the confusion. The patient often becomes worse during evening/night time. An important sign is that there has been a change in the mental or psychological state of the person over a relatively short period of time.

Terminal Respiratory Secretions
Secretions pooling in the pharynx in the last days or hours of life may cause noisy breathing (“death rattle”). There is limited evidence for the efficacy of anticholinergics, a lack of evidence for the superiority of one agent over another (hyoscine butylbromide, hyoscine hydrobromide, glycopyrronium) and whilst they may reduce the production of further secretions, they do not reduce those already present. There is a substantial cost difference, with hyoscine butylbromide being considerably cheaper than the others.

Providing explanation and reassurance to the family on what can be a distressing symptom, is as, or more, important than drug treatment. Non-drug management such as positioning of the patient, to drain secretions is also an aid to management.

Pharmaceutical Care
In the last few days the patients’ ability to take their medication may fluctuate as will the carers’ ability to manage any necessary changes in therapy. Pharmacists can provide practical support and advice to help patients and their families at this time. The potential problems which pharmacists can help to address are outlined in the table overleaf.
### Last days of life

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuating level of consciousness</td>
<td>Verify treatment of all main symptoms are available via non-oral route either as required or regularly as appropriate for the patient and the care setting</td>
<td>• Continued control of symptoms</td>
</tr>
<tr>
<td>Unable to take medicine orally and cannot be given by another route</td>
<td>Monitor for signs of withdrawal. Sedate if signs are severe</td>
<td>• Prevent suffering</td>
</tr>
<tr>
<td>Multiple medicines delivered via subcutaneous infusion</td>
<td>Verify medicines are stable/compatible and are appropriately diluted</td>
<td>• Patient receives correct dose of medicine and is not harmed by infusion of degredants or precipitate</td>
</tr>
<tr>
<td>Altered long term aims of treatment</td>
<td>Advise stopping all medication which gives no short term benefit to the patient Explain to/reassure patient carer about this</td>
<td>• Avoid unnecessary treatment</td>
</tr>
<tr>
<td>Continuing need for effective symptom control</td>
<td>Review for ongoing symptom control and any new symptoms. Adjust or initiate therapy accordingly</td>
<td>• Effective control of all symptoms</td>
</tr>
<tr>
<td>Ongoing monitoring of medicine therapy</td>
<td>Monitor patient’s condition and adjust ongoing medicine therapy accordingly, verify invasive investigations avoided unless they will give definite short term benefit</td>
<td>• Effective medicine treatment without causing unnecessary discomfort to patient</td>
</tr>
<tr>
<td>Restlessness/agitation not responding to reassurance and underlying cause unclear or not appropriate to treat</td>
<td>Advise sedation with midazolam or haloperidol is initiated</td>
<td>• Reduce distress of patient, their family and friends</td>
</tr>
<tr>
<td>Communication: discuss decision with family and friends</td>
<td></td>
<td>• Promote understanding, obtain agreement, allow farewells before patient becomes unable to respond to their presence</td>
</tr>
</tbody>
</table>

### Pharmaceutical care plan

- Verify treatment of all main symptoms are available via non-oral route either as required or regularly as appropriate for the patient and the care setting
- Monitor for signs of withdrawal. Sedate if signs are severe
- Verify medicines are stable/compatible and are appropriately diluted
- Advise stopping all medication which gives no short term benefit to the patient. Explain to/reassure patient carer about this
- Review for ongoing symptom control and any new symptoms. Adjust or initiate therapy accordingly
- Monitor patient’s condition and adjust ongoing medicine therapy accordingly, verify invasive investigations avoided unless they will give definite short term benefit
- Advise sedation with midazolam or haloperidol is initiated
- Communication: discuss decision with family and friends
### Pharmaceutical care plan (continued)

<table>
<thead>
<tr>
<th>Issue</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/little intake of food or drink</td>
<td>Advise on the pros and cons of initiating parenteral fluid</td>
<td>• Ensure that only started if appropriate, i.e. to avoid opioid toxicity, prevent thirst, renal failure. Avoid when it will produce unnecessary physical barriers to family and friends and if not wanted by the patient</td>
</tr>
<tr>
<td></td>
<td>Maintain regular mouth care</td>
<td>• Promote comfort</td>
</tr>
<tr>
<td>Potential haemorrhage</td>
<td>Verify ‘as required’ strong opioid and benzodiazepine are available to be given by intramuscular or intravenous bolus</td>
<td>• Sedate patient and minimise suffering</td>
</tr>
<tr>
<td>Wound care in last 48 hours</td>
<td>Reduce dressing frequency. Advise on use of dressings designed to protect wound. Avoid very regular turning.</td>
<td>• Minimise discomfort</td>
</tr>
<tr>
<td>Patient’s family and friends understanding and emotions</td>
<td>Communicate: careful explanation and discussion of medicine treatments</td>
<td>• Calm fears, obtain permission, and allow expression of emotions</td>
</tr>
<tr>
<td></td>
<td>Involve family in simple tasks such as mouth care, feeding, bathing</td>
<td>• Reduce feelings of helplessness</td>
</tr>
<tr>
<td>Continuing risk of convulsion into last 48 hours</td>
<td>Verify anticonvulsant therapy prescribed by non-oral route if patient unable to swallow or likely to become so</td>
<td>• Prevent terminal convulsions</td>
</tr>
<tr>
<td></td>
<td>Verify measures put in place to treat fits if they occur</td>
<td>• Rapid treatment of convulsions</td>
</tr>
<tr>
<td>Patient needs to communicate</td>
<td>Advise a reduction in sedation</td>
<td>• Allow clear communication</td>
</tr>
</tbody>
</table>
**Service Frameworks and Advanced Care Planning**

The symptoms which patients experience and the services required during end of life care can often be anticipated and advanced care planning is strongly advocated. This document highlights a large number of service developments and makes recommendations for the way ahead for delivering palliative care services in Scotland.

The Gold Standards Framework (GSF), developed by GP Dr Keri Thomas in West Yorkshire, aims to assist practitioners within the primary care setting in improving the organisation of care for those with a cancer diagnosis in the last year of life. In Scotland the framework has been modified to meet the needs of patients from diagnosis onwards. There are seven key principles within the Gold Standards Framework and these are: Communication, Co-ordination, Control of symptoms, Continuity of care, Continued learning, Carer support and Care of the dying.

The use of integrated care pathways for the care of the dying is increasing as a method for extending implementation of the hospice model of palliative care into other care settings. The multi-disciplinary documents provide an evidence based, detailed framework and method of recording and measuring outcomes of care. The most widely implemented of these pathways is the Liverpool Care Pathway for the Dying Patient developed at the Marie Curie Institute of Palliative Care, Liverpool University. Work is ongoing for the transfer of this approach to non-malignant conditions and to address particular needs in the paediatric population.

The adoption of the NHS Lothian Do Not Attempt Resuscitation (DNAR) policy throughout Scotland should also aim to clarify roles and responsibilities of healthcare professionals in relation to expected deaths of palliative care patients. The framework involves clarity of the police and procurator fiscal’s procedures in investigating deaths where a DNAR is in place.

Every adult with mental capacity has the right to agree to or refuse medical treatment. A living will can be used to make wishes clear in advance. Living wills can include general statements about wishes, which aren’t legally binding, and specific refusals of treatment called ‘advanced decisions’ or ‘advance directives’.

**Out of Hours Care - Access to Medicines**

Patients require to opt out of the system permitting sharing of core information, the emergency care summary, with out of hours medical services which includes a list of their current prescription medication. Community pharmacists can access this information via NHS24, provided the patient gives permission at the time. Pharmacy services within primary care assist through the development of Community Pharmacy Palliative Care Network Pharmacies. These services were developed initially through the Pharmaceutical Care Model Schemes. Community pharmacies maintain a core range of palliative care medicines as well as providing enhanced levels of service to palliative care patients and their carers and in some Boards these medicines can be accessed during out of hours periods. Out of hours emergency centres may also hold palliative care medicines but the main emphasis is on planning ahead to prevent problems out of hours.
Disposal of Unwanted Medicines

Patients may be prescribed more medicines in the final stages of life than at any other time. Consequently, soon after a death, relatives may return what seems to be a huge quantity of medicines for disposal. Pharmacy staff need to be aware of and sensitive to the needs of bereaved relatives at this time. It may be helpful for pharmacists to be aware of the SEHD publication What to Do after a Death in Scotland. It is available to download at the following link www.scotland.gov.uk/Resource/Doc/47133/0025575.pdf. Pharmacists may be contacted for advice regarding disposal of medicines after a patient has died, particularly where there may be concerns around potential for misuse of the medicines if they were to remain in the home.

Now read Section 11 ‘The last 48 hours’ in The ABC of Palliative Care (second edition) included with this pack
Summary of article

- In the last 48 hours patients experience:
  - increasing weakness and immobility
  - loss of interest in food and drink
  - difficulty in swallowing
  - drowsiness.
- Treatment of symptoms is based on clinical findings rather than investigations.
- Review the need for prescribed medicines, continuing only those treatments required to control symptoms; many patients will not manage oral therapy.
- Previously ‘essential’ medicines such as antihypertensives, corticosteroids, antidepressants and hypoglycaemics are often no longer needed and analgesic, antiemetic, sedative and anticonvulsant medicines form the new ‘essential’ list to work from.
- Address the symptom of breathlessness and the fear and anxiety that may accompany it.
- Treat acute restlessness and confusion whilst addressing the underlying cause.
- Noisy respiration may be helped by repositioning the patient and, if substantial secretions are present, by giving hyoscine butylbromide.
- Causes of restlessness and confusion include:
  - medicines
  - physical causes
  - metabolic upset
  - anxiety and distress.
- Most emergencies in the last 48 hours are irreversible and treatment should be aimed at urgent relief of distress and concomitant symptoms, available for immediate administration if necessary.
- Symptoms likely to be prevalent in the last 48 hours of life for an advanced cancer patient are pain, dyspnoea, restlessness, agitation, constipation, anorexia, weight loss, dry mouth, nausea and vomiting. In general, patients become weaker and their level of consciousness falls.
- Don’t stop opioids, benzodiazepines or antidepressants suddenly as this can lead to a distressing withdrawal syndrome. Sudden withdrawal of anticonvulsants may precipitate seizures.
- Don’t give intravenous treatments, antibiotics, introduce nasogastric or percutaneous endoscopic gastrostomy tubes, start long acting opioids, use artificial respiration or resuscitate.
- The use of hydration is very controversial. Most patients will not benefit unless they are opioid toxic as a result of dehydration or are at risk of this. There is no evidence to show whether or not hydration has any effect on thirst. The balance of need versus intrusion must be decided in each individual case.
Activity 1
Mr H is a 56 year old man who was diagnosed as having non-small cell carcinoma two years ago. His disease has progressed during this time and control of symptoms has been crucial to maintaining a reasonable quality of life. He has had ongoing problems with breathlessness and it is likely that he has cranial metastases. His chest is ‘crackly’ and he has difficulty in expectorating thick, yellow sputum.

In the last 48-72 hours, Mr H has become increasingly weak. He is unable to leave his bed and is dependent on his wife, daughter and district nurse for all his care. He is often drowsy and disorientated, when awake. Mr H is still smoking 10-20 cigarettes per day but managing to eat or drink little.

His drug treatment at present is:
- Dexamethasone 4mg oral twice a day
- Salbutamol inhaler 200 micrograms four times a day
- Ipratropium inhaler 40 micrograms four times a day
- Fentanyl 50 microgram/hour transdermal patch applied every three days
- Morphine sulphate immediate release solution 30mg when required to relieve breakthrough pain
- Co-danthrusate capsules three at night
- Furosemide 40mg in the morning
- Gliclazide 80mg half an hour before breakfast
- Paroxetine 30mg at night

1. What changes need to be made to his existing treatment now?
Twenty four hours later, Mr H’s level of consciousness is falling gradually. He has not eaten or drunk for over 48 hours. This is distressing his wife and daughter. He is also moaning and is obviously restless. His breathing is becoming noisy. This is also distressing Mr H’s wife and daughter.

2. Should intravenous or subcutaneous hydration be started now?

3. What may be making Mr H restless or uncomfortable?

4. How could the noisy breathing be handled?
Suggested answers

Activity 1

1. What changes need to be made to his existing treatment now?
   *Stop gliclazide, since Mr H is no longer eating.*

   Steroid may be for either treatment of raised intracranial pressure due to cranial metastases or for breathlessness. It is necessary for symptom control and should be continued as long as Mr H can tolerate oral therapy. If intracranial pressure rises, Mr H may have a seizure. Diazepam 10mg as rectal tubes could be prescribed and supplied. Mr H’s wife and daughter will need to be shown how to administer these. An alternative, if this route is considered unacceptable to the patient or his family, is buccal midazolam liquid 10mg/ml (unlicensed preparation).

   Salbutamol and ipratropium should be given by nebuliser. Mr H’s wife and daughter will need to be shown how to use the nebuliser and keep the mask and chamber clean. They should also be advised to mix the two drugs together. The use of mouthpieces in patients with fluctuating levels of consciousness is not practical, so a mask should be issued instead.

   Continue to give co-danthrusate as long as Mr H can tolerate oral therapy. If unable, the Community Nurse will review each day to ensure that Mr H does not become uncomfortable due to constipation. If constipated, then treat with enemas/suppositories if necessary.

   Stop furosemide to prevent frequent diuresis and the need for the use of bed pans or catheter UNLESS pulmonary oedema is present, in which case continue.

   Continue paroxetine until patient becomes unable to take oral therapy to avoid withdrawal reaction.

   Continue with fentanyl. Provide breakthrough as diamorphine 10mg subcutaneous bolus as well so that if in pain and unable to take oral therapy can be given by attending nurse or doctor.

   Ability to take medicines will change from hour to hour and must be reviewed regularly.

   He should not be started on antibiotics for his chest infection as they will not have time to be effective and may make Mr H nauseous. He may also have difficulty taking them orally, which would necessitate intravenous therapy which would be intrusive and difficult to manage practically at home.

2. Should intravenous or subcutaneous hydration be started now?
   *Intravenous therapy is not appropriate for the home setting however subcutaneous infusions have been used successfully and safely.*

   Hydration will not prolong survival and its ability to influence symptoms has not been proven one way or the other.

   Careful discussion with the family over what they expect to gain from this treatment and what is possible is necessary. They will need to be closely involved in deciding if this is the right course of action to take.
3. What may be making Mr H restless or uncomfortable?
- Medicine withdrawal (SSRIs, nicotine)
- Looking for reassurance or company
- Pain
- Opioid toxicity
- Difficulty in breathing
- Development of a pressure sore
- Distended bladder
- Constipation
- Inability to move due to weakness
- Cerebral anoxia
- Anxiety/anguish, delirium.

4. How could the noisy breathing be handled?
If due to secretions pooled in the lower respiratory tract then careful positioning, the use of hyoscine hydrobromide (which can exacerbate agitation) or hyoscine butylbromide and the use of suction will help.

If due to noisy tachypnoea then give additional diamorphine 10mg SC or morphine sulphate immediate release solution 30mg to reduce frequency of breaths.
References


Additional references


Chapter 12 Legal and ethical issues in palliative care
Objectives

On completion of this chapter you should be able to:

• outline the key principles of the Adults with Incapacity (Scotland) Act 2000 in relation to palliative care

• list the information required for palliative care patients travelling abroad with Controlled Drugs

• explain the principles of unlicensed medicines use in palliative care

• explain the key recommendations of the Shipman Inquiry in relation to the use of controlled drugs in palliative care

• explain the current position in relation to physician assisted suicide.
Chapter 12
Legal and ethical issues in palliative care

This section has been included to highlight important legal and ethical issues with are associated with patients with terminal illnesses.

The section includes information on:
- The Adults with Incapacity (Scotland) Act 2000
- Travelling abroad with Controlled Drugs
- Unlicensed medicine use in palliative care
- The Shipman Inquiry

Adults with Incapacity (Scotland) Act 2000

The Adults with Incapacity (Scotland) Act 2000 provides a framework for safeguarding the welfare and managing the finances of adults who lack capacity due to mental disorder or inability to communicate. This may include patients at the end of life who are unable to communicate, patients who are unconscious or those with cognitive impairment (e.g. dementia or extensive brain metastasis).

The Act aims to protect those who lack capacity to make particular decisions, but also to support their involvement in making decisions about their own lives as far as possible. Anyone authorised to make decisions made on behalf of someone with impaired capacity - referred to as a ‘proxy’ - must apply the following principles:

1. Benefit - The person must benefit from the action/decision. Furthermore benefit should not be reasonably achievable without it.
2. Least restrictive option - any action/decision should be the minimum action necessary to achieve the purpose and should maintain the person’s freedom as far as possible.
3. Takes account of the wishes of the person - the present and past wishes and feelings of the person must be considered, recognising that some adults will be capable of expressing wishes and feelings but not taking a particular action/decision.
4. Consultation with relevant others - those with an interest in the patient’s welfare should be consulted. For example, their main carer, a close relative or their attorney.
5. Encourage the person to use existing skills and develop new skills.

It must be recognised that people with palliative care needs may not wish to proceed with active treatment (e.g. chemotherapy). If chemotherapy or other therapies are with palliative intent they may only extend the patient’s survival by a few weeks or months. Some patients may consider this to be unacceptable when balanced against undesirable side-effects and reduced quality of life. The person must always be presented with all the information to enable them to make an informed choice.

A short guide to the Act is available at www.scotland.gov.uk Publications/2008/03/25120154/1
Information for patients travelling abroad with Controlled Drugs

Patients who are prescribed Controlled Drugs and plan to travel outwith the UK need to be aware of the regulations for exporting these medications from the UK and importing them into the destination country.

Regulations regarding travelling with Controlled Drugs can change and it is advisable to contact the Home Office for the latest advice well in advance of travel. They can be contacted directly or on-line via their website.

The Home Office
Drugs Licensing Section
6th Floor, Peel Building
2 Marsham Street
London
SW1P 4DF

Tel: 020 7035 0484
Fax: 020 7035 6161
Email: licensing_enquiry.aadu@homeoffice.gsi.gov.uk

If an export licence is required an application should be made to the Home Office at least two weeks prior to the date of travel. An application form can be downloaded from: http://www.drugs.homeoffice.gov.uk/drugs-laws/licensing/personal/

Note: A personal licence has no legal standing outside of the UK.

Patients should be advised to contact the Embassy/Consulate/High Commission of the country of destination (remembering countries stopped at on route) regarding local policy on the importation of Controlled Drugs. Embassy contact details are available on the Home Office website.

UK customs regulations were simplified in 2008. Subsequently it is the restrictions imposed by the destination country that are likely to present limitations.

It is important that patients traveling with Controlled Drugs carry a letter issued by the prescribing doctor, which should contain the following information:

- patient name, address and date of birth
- the outward and return dates of travel
- the country of destination
- a list of the medications carried including dosages and total amounts.

Controlled Drugs should be in their original packaging and carried in hand luggage along with the covering letter/export licence. It is advisable to contact BAA and the Airline regarding their regulations.
The International Narcotics Control Board has produced a list of suggested maximum quantities for personal import/export of internationally controlled substances.

Additional information can be obtained from:

http://drugs.homeoffice.gov.uk/drugs-laws/licensing/personal/


http://www.incb.org/incb/guidelines_travellers.html

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**Practice Points**

- Consideration should be given to the maximum quantity of medication that can be dispensed on the NHS. A private prescription may be necessary for longer periods of travel.
- The Controlled Drugs prescribed may not be available in the destination country. A local hospice may be able to advise.
- Some countries do not permit the importation of certain commonly used opioids e.g. diamorphine, dihydrocodeine, codeine.
- It may be necessary to switch to an alternative medication that is readily available in that country.
- If an export licence is required, contact the Home Office directly to ensure that they have received the application form and that it contains the necessary information.
- If a patient will be away for more than 3 months they should be advised to register with a GP in the destination country to obtain further supplies of medication.
Unlicensed medicine use within palliative care

In palliative care there are two situations that arise:

1. “Off-label” use
   As a result of licensing restrictions, it is common to use licensed medicines for an unlicensed indication, by an unlicensed route or as an unlicensed dose. Such use can be supported by experience in clinical practice and accepted reference sources such as The Oxford Textbook of Palliative Medicine or The Palliative Care Formulary. This practice is commonplace in palliative care.

2. Unlicensed medicines or formulations
   Occasionally it may be necessary to prescribe a medicine which has no marketing authorisation in the UK e.g. thalidomide for night sweats, or to use a formulation which has no marketing authorisation e.g. hydromorphone injection.

It is important to understand that the licensing process regulates the activities of pharmaceutical companies and not the prescribing practice of a qualified prescriber. This prescribing practice is supported by the Medicines Act 1968 which permits a prescriber to prescribe unlicensed medications provided they act with reasonable care and in a way consistent with the rest of their profession whilst balancing the benefit and harm of the treatment. The supplying pharmacist also assumes some responsibility for any adverse effects suffered.

The General Medical Council and medical defence organisations have suggested obtaining informed patient consent, however, the use of drugs outwith license in palliative care is so widespread that this is not always practical and may lead to increased patient anxiety.

The RPSGB has produced a factsheet on the use of unlicensed medicines in pharmacy www.rpsgb.org/pdfs/factsheet5.pdf
The Shipman Inquiry

Harold Shipman was convicted on 31st January 2000 of the murder of 15 patients whilst he was a GP in Manchester and one count of forging a will. He was subsequently sentenced to life imprisonment.

The Inquiry’s Sixth and final report, was published on 27th January 2005. The management and regulation of controlled drugs was considered in the Fourth report www.the-shipman-inquiry.org.uk/fourthreport.asp

Recommendations for change affecting pharmacy practice:
- Permitting pharmacists to amend specified aspects of a Controlled Drug prescription to render it legal provided that the intent is clear and the pharmacist is willing to take full professional responsibility for their actions.
- Changes to the process of collection of Schedule 2 Controlled Drugs from the pharmacy including the request for identification from the person collecting if this is a patient’s representative.
- Recording the name of any healthcare professional who collects Controlled Drugs for a patient.
- Recording the name and obtaining the signature on the back of the prescription form of any person collecting Schedules 3 or 4 Controlled Drugs.
- Permitting electronic Controlled Drug registers.
- Extending the length of time it is legally required for a pharmacy to keep copies of the Controlled Drug register.

Recommendations for change affecting community services:
- Pharmacists should prepare a statutory patient drug record card (PDRC) for all injectable Schedule 2 Controlled Drugs being dispensed.
- Healthcare professionals who administer Schedule 2 Controlled Drugs should enter every administration and keep a running balance of the remaining stock. After the death of the patient or discontinuation of treatment the administration record should be sent to the primary care trust and then inspected for anomalies.
- Change in the law so that Controlled Drugs would become property of the Crown on patients’ death.
- Increased formality of destruction of injectable Schedule 2 Controlled Drugs.
- Primary care organisations should assume responsibility for the appropriate destruction of Controlled Drugs.

Ethical principles
Medical ethics is based on four common, prima facie moral commitments – respect for autonomy, beneficence, non-maleficence and justice. These principles offer a common moral framework and language, which helps healthcare workers to make decisions while reflecting on moral issues.

Physician assisted suicide
In 2008 Washington became the second US state to legalise physician assisted suicide. The state of Oregon enacted the Death with Dignity Act in 1997 and over a period of ten years 341 people have used it to end their lives. More have obtained the prescription and never used it. The act allows physicians to prescribe a lethal dose of medication for adult patients who are mentally competent and have a prognosis of less than six months. The patient must make an oral and a written request to their physician expressing their wish to die. The patient must then wait at least 15 days before reiterating the oral request. Two physicians must approve the request and the patient must self-administer the lethal dose. The patient may revoke their request at any time. If the physician suspects the patient has a disorder causing impaired judgement then the patient must first be referred for counselling. www.oregon.gov/DHS/ph/pas/docs/statute.pdf

Physician assisted suicide is also legal in the Netherlands, Belgium and Switzerland. Unlike other countries Swiss law does not require the patient to be resident there to end their life. Under UK law and the Suicide Act 1961 and the Persons Act 1861 there is still a risk of prosecution for family members or carers who assist the patient to travel to Switzerland to commit suicide.

A Bill proposed by Lord Joffe to legalise physician assisted suicide in the UK was rejected by the House of Lords in 2006. The Assisted Dying for the Terminally Ill Bill proposed to enable a terminally ill adult to receive medical assistance to die. Many religious groups and the Care not Killing group opposed the Bill, as did The Royal College of Physicians and the Royal College of General Practitioners.

In December 2008, MSP Margo MacDonald lodged a Member’s Bill on End of Life Choices. The proposed Bill aims to clarify the law in Scotland with regard to physician assisted dying when a person wishes to end their life. This Bill reached the consultation stage in April 2009.

The debate continues and pharmacists should consider their ethical and professional boundaries. It is proposed that the physician will prescribe the lethal medication and the patient will self-administer but who will dispense the medication? Should pharmacists legally be made aware of the intent of the prescription so that they may decide whether they wish to be involved? Inevitably any legislation will conflict with personal beliefs for some pharmacists. The RPSGB remains neutral. Pharmacists would require training on end of life care and would require a clause to enable those who are not willing to participate to opt out.
Additional references

- Gillon R. Medical ethics: four principles plus attention to scope. BMJ 1994;309:184
- Meek C. Pharmacy and assisted suicide: what can be learnt from experience abroad? The Pharmaceutical Journal. 2006;277:639
- Meek C. Pharmacy involvement where assisted suicide and euthanasia are permitted. The Pharmaceutical Journal. 2006;277:614
- http://www.rpsgb.org.uk
- http://www.the-shipman-inquiry.org.uk

Activity 1
Identify medicines that are commonly used ‘off-license’ in palliative care.
Activity 2
Determine the suggested maximum quantities of controlled substances that are permitted for international travellers.
Chapter 13  Medicine delivery systems
Objectives

On completion of this chapter you should be able to:

- list medicine delivery systems and describe their role in palliative care
- describe the person responsible in your area, for the distribution and maintenance of four medicine delivery systems
- recommend dose conversions (from oral opioids) for medicines administered by subcutaneous infusions via a syringe driver/pump.
Chapter 13
Medicine delivery systems

Medicine delivery systems
This section has been included in the distance learning pack to highlight the range of medicine delivery systems used for the administration of medicines for symptom control in palliative care. The term ‘medicine delivery systems’ is all encompassing and includes highly technical medicine administration (e.g. spinal) as well as commonly used administration routes in other specialities (e.g. nebulisation).

Descriptions of the use of the following medicine delivery systems in palliative care have been included:
- syringe drivers/pumps
- nebulisers and medical gases
- subcutaneous hydration
- fentanyl transdermal patches
- spinal medicine administration.

Please read each section before attempting the activities.

Syringe drivers/pumps
Intravenous medicine administration should be avoided in palliative care patients because it is invasive and no more effective than the subcutaneous route. The intramuscular route should also be avoided especially in cachectic patients as it is painful.

The subcutaneous route should not only be reserved for use in a dying patient but should be considered early in the management plan if symptoms are problematic.

The subcutaneous parenteral route is used when the oral route is not available or if it becomes impractical due to:
- inability to swallow
- nausea and/or vomiting
- intestinal obstruction
- poor absorption e.g. ileostomy
- patients who are very drowsy, comatose or semi-comatose
- patients whose analgesic requirements would involve the use of an excessive number of tablets (although this is unusual).

The oral route should be reinstated if or when possible.
The subcutaneous route is the parenteral route of choice in palliative care patients. Continuous subcutaneous infusions are preferred for the following reasons:

- more comfortable for the patient
- avoids the risks of infection with prolonged intravenous administration
- easily administered especially in patients with poor veins or little muscle bulk
- avoids the need for frequent injections
- can be used for prolonged periods of time. Cannula can remain in place for 72 hours or longer if there is no evidence of redness or inflammation at the site.

The areas used to site the subcutaneous injection are:

- the anterior aspect of the upper arms
- the anterior abdominal wall
- the anterior aspect of the thigh
- the scapula
- or rarely the anterior chest wall.
Use of infusion devices

The portable syringe driver/pump is the infusion device commonly used in palliative care. The syringe driver/pump allows small volume infusions to be administered via a cannula/needle (butterfly) sited under the skin. A range of syringe drivers/pump are available, most of them being battery operated, non-bulky and readily portable.

There are important differences in the method of operation of these, particularly in setting the delivery rate. It is therefore imperative that the operator is fully trained before using any syringe driver/pump. Fatal drug administration errors have been reported and are due to unfamiliarity of the operator with a particular syringe driver/pump and subsequent misuse of it, or confusion due to similarities between the models commonly used1-3.

NB: This distance learning pack will not cover the setting up of the syringe driver/pump. It is recommended that all staff using syringe drivers should be fully trained in their correct use.

Syringe drivers/pumps

The most commonly used devices in palliative care in the UK are Graseby syringe drivers and McKinley T34 syringe pumps. There are two Graseby models available – the MS16A (blue panel) and the MS26 (green panel). The main difference between these two models is the rate setting for the 24 hour continuous infusion.

- MS16A Graseby syringe driver (blue panel) delivers the subcutaneous infusion at a rate of mm per hour.
- MS26 Graseby syringe driver (green panel) has a delivery rate of mm per 24 hours.
- A 20ml or 30ml syringe is commonly used with Graseby MS16A and MS26 syringe drivers. This allows a more dilute infusion to minimise subcutaneous site irritancy and is useful if a particular combination of medicines requires a larger volume to ensure compatibility.

The McKinley T34 syringe pump is more commonly used now in Scotland. This pump is calibrated in mls per hour. 20ml or 30ml luer lock syringes (suggested brand BD Plastipak) can be used with the lockbox which is supplied with each pump. Fine bore lines with a small priming volume should be used. In some areas, these may include anti-syphon valves. If anti-syphon lines are not available then the device should be placed lower than or at the same level as the infusion site.
Sites of administration
The subcutaneous tissues of the pectoral region and anterior abdominal wall are most frequently chosen, but a change of site may be necessary in the event of a local reaction, seen as small areas of redness and swelling at the injection site. This can occur in patients who are receiving high doses of diamorphine or irritant drugs (e.g. cyclizine) and may be due to chemical irritancy, pH, osmolality or a degradation product.

Medicines administered via syringe drivers/pumps
Diamorphine is the opioid of choice for subcutaneous administration due to its high water solubility compared with morphine, however, several areas have been using morphine first line due to the recent shortage of diamorphine. Diamorphine allows small volume infusions to be used. Based on clinical practice, it is estimated that subcutaneous diamorphine is approximately three times as potent as oral morphine.

Therefore, to convert from oral morphine to subcutaneous diamorphine:
- add up the total oral morphine requirements (both regular and breakthrough) over the previous 24 hours
- divide this dose by three (this dose may need to be adjusted according to the clinical situation)
- the calculated amount of diamorphine should be prescribed over 24 hours as a continuous subcutaneous infusion
- breakthrough analgesia should still be prescribed and is given as 1/6th of the total 24 hours subcutaneous dose as required by subcutaneous bolus injections.

A range of medicines other than diamorphine are administered via syringe drivers/pumps. Medicines used to treat nausea, vomiting, terminal secretions, and agitation are commonly used. Irritant medicines (e.g. diazepam, chlorpromazine and prochlorperazine) should not be administered subcutaneously.

Compatibility/Stability of admixtures for subcutaneous infusion
In the United Kingdom, it is common practice to administer 1, 2 or 3 different medicines in the same syringe. Combinations with 4 or 5 medicines are generally discouraged and only used when there are no other treatment options available.

The stability and compatibility of combinations of medicines should always be confirmed, particularly as the small infusion volume means that the medicines delivered may be very concentrated.
It is important to ascertain if the compatibility data available is relevant to the situation of intended use:

- Medicine combinations may be compatible at certain concentrations but not at others, thus the concentration of each medicine in the solution should be compared and not the dose. The diluent used and the time period for the infusion should also be checked because different diluents and longer infusion periods may also cause compatibility problems. Water for injection (WFI) or sodium chloride 0.9% are generally used as diluents in the UK. WFI is the preferred first line for combinations of 2 or more medicines in one syringe as some commonly used medicines e.g. cyclizine is incompatible with sodium chloride.

- pH is one of the main predictors of whether two or more medicines to be mixed are likely to be compatible. Most of the medicines used by subcutaneous infusion are acidic, but a few are alkaline (e.g. diclofenac) and the latter therefore usually need to be given via a separate infusion.

There are different classes of medicine compatibility data:

**Physical compatibility**
If mixing 2 or more medicines does not result in a physical change e.g. discolouration, clouding, or crystallisation, they are said to be physically compatible.

**Observational data**
Data obtained from health care professionals about the visual appearance of various medicines mixtures over the infusion period (generally 24 hours). This is subjective and imprecise; generally only major incompatibilities can be identified in this way.

**Laboratory data**
These are generally derived from microscopic examination of a medicine mixture under polarised light at specified concentrations and several time points when kept under controlled conditions. Although more robust, these are not definitive; a solution may remain physically clear even when there is a chemical incompatibility.

**Chemical compatibility**
If mixing two or more medicines does not result in a chemical change leading to loss or degradation of one or more of the medicines, the mixture is said to be chemically compatible. Chemical compatibility data is generally obtained by analysing the medicine mixture by high performance liquid chromatography (HPLC) at specified concentrations and several time points when kept under controlled conditions.
Annex 1 of the SIGN guideline No. 106 Control of Pain in Adults with Cancer outlines peer-reviewed stability studies of two and three drug diamorphine combinations. Stability and compatibility information can also be obtained from local guidelines and from palliative care specialists.

In general it is considered good practice to:

- dilute infusion mixtures as much as possible (note that the maximum volume which will fit in syringe pumps is often less than the maximum nominal syringe volume, due to the design of the pumps e.g. the maximum volume which can be used in a 30ml syringe in a McKinley T34 pump is 22ml)
- use any medicine combination within 24 hours of preparation
- check the contents of the syringe and tubing by visual inspection at regular intervals to attempt to detect any colour change, cloudiness, precipitation, gas bubbles, etc.
- protect the mixture from direct sunlight as some of the medicines will degrade more rapidly in sunlight.
- protect the mixture from extremes of temperature. For example, avoid placing the pump under the bedclothes, or near to a heat source.

**Practice Points**

Locate your local guidance on the use of subcutaneous medicines in palliative care.

**Supplies of medicines and syringe drivers/pumps in primary care**

Good discharge planning is imperative to ensure continuity of supply of medicines when patients are at home. Palliative care community pharmacy networks have been set up in most areas as a result of the Model Schemes initiative to ensure timely and 24 hour access to palliative care medicines and specialist advice.

NHS QIS Cancer standards 2001 includes standards on symptom management, access to medicines and equipment and guidelines on the use of syringe drivers/pumps and medicines used in syringe drivers/pumps.

Arrangements for management of syringe drivers/pumps vary between Health Boards and includes distribution via local surgeries, community hospitals, Community Health and Care Partnerships or hospices. Systems need to be in place to ensure that syringe drivers/pumps are managed safely. Guidance on infusion systems is available from the Medicines and Healthcare products Regulatory Agency (MHRA). A standard for the use of syringe drivers/pumps in palliative care has been developed by the Scottish Palliative Care Pharmacist’s Association (SPCPA).
Nebulisers and medical gases

The aim of nebuliser therapy is to convert a solution of a medicine into an aerosol for inhalation, so that a therapeutic dose can be administered within a short period of time. Nebulisers are used when:

- a large dose of medicine is required
- co-ordinated breathing is difficult
- hand held inhalers are ineffective
- the medicine is not available as an inhaler.

No effort is required by the patient during use, just normal steady breathing.

Jet nebulisers, powered by an electric compressor, are the type of nebuliser most frequently used in the community. The nebuliser unit is connected to the compressor via plastic tubing which also connects it to a mask or mouthpiece for delivery of the nebuliser solution to the patient. A volume of between 2ml and 4ml of solution is usually nebulised each time. The volume of solution must not exceed the maximum fill volume for the nebuliser chamber. Nebulisation of up to 4ml of solution takes about 10 minutes. The nebulisers usually leave about 0.5ml residual solution after nebulisation.

Patients should have information on:

- how to assemble and set up the nebuliser
- how to clean and sterilise components of the nebuliser
- how frequently and where to have the nebuliser serviced
- what volumes of medicine to nebulise
- what to do if treatment is ineffective or there is equipment failure.

The nebuliser and mask/mouthpiece should be washed in warm water and detergent, then rinsed and dried well. Ideally this should be after every use but at least once daily. The nebuliser should be reconnected and run dry for a few moments after cleaning to make sure the equipment is dry\(^1,2\).
Use of nebulisers in palliative care

A range of medicines are used in palliative care:

- Sodium chloride 0.9% is nebulised to loosen tenacious secretions.

- Bronchodilators (e.g. salbutamol) are used for treatment of breathlessness due to reversible airway obstruction.

- Local anaesthetics (e.g. lidocaine 2% or bupivacaine 0.25%) can be used for the treatment of non-productive cough. There is a risk of bronchospasm and reduced cough reflex after administration. Salbutamol should be given prior to treatment. Patients should be advised not to eat or drink for about an hour after treatment because numbing of the mouth could cause swallowing difficulties and aspiration due to reduced cough reflex. In addition, patients may be unaware of heat from food/drink which can lead to severe burns.

Subcutaneous hydration

Hypodermoclysis, the subcutaneous infusion of fluids, is a safe and effective technique for treating dehydration. It is less invasive than intravenous therapy, technically easier to carry out and in palliative care is used in preference to intravenous administration. Controversy exists around the issue of hydration of patients in their final days. There are arguments for and against hydration although there is a paucity of evidence to support both views.

Increasingly, hypodermoclysis is used in palliative care when an adequate intake of oral fluid is not feasible and the patient is symptomatic from dehydration. This may result in symptoms of fluid depletion (weakness, postural hypotension, thirst (not simply dry mouth)) or resultant poor clearance of drugs and their metabolites (particularly opioids) causing symptoms of toxicity such as confusion, delirium or restlessness.

Contra-indications to the subcutaneous infusion of fluids include:

- generalised oedema
- major coagulation disorders
- patients who already have an indwelling intravenous catheter
- caution in patients with pre-existing heart disorders
- caution in patients with low albumin levels as this can lead to increased presence of oedema.
Prescribing of solutions for subcutaneous administration:

- A doctor or non-medical prescriber should prescribe solutions for subcutaneous administration.

- The volume and type of infusion solution prescribed depends on the patients’ requirements. 500ml to 1000ml administered overnight is often adequate to maintain hydration in the palliative care setting³,⁴

- Solutions suitable for administration include:
  - sodium chloride 0.9% infusion BP
  - glucose 5% infusion BP

Glucose 5% is used on rare occasions in patients who are hypernatraemic: there is a theoretical risk that glucose 5% may draw fluid into the interstitial space and cause sloughing of skin – it has however been used successfully in clinical practice.

If indicated, hyaluronidase may be prescribed for patients in whom the absorption of subcutaneous fluid is consistently poor, despite rotating subcutaneous sites for administration. Hyaluronidase 1500 units subcutaneous injection (dissolved in 1ml water for injection) may be injected through the butterfly once daily, immediately prior to the start of infusion. NB: severe allergic reactions have been reported with the use of hyaluronidase³.

Rate of infusion

The solution should be infused by gravity. Infusion rates from 20 to 125ml/hour are well tolerated³,⁴. The formula shown below may be used to calculate the flow rate.

\[
\text{Drops/minute} = \frac{\text{total volume to be infused (ml) } \times \text{ drops/ml}^*}{\text{total infusion period (minutes)}}
\]

* The drops/ml value is found on the reverse of the packaging for intravenous giving sets.

Equipment required for hypodermoclysis:

- 25 gauge butterfly infusion set (a teflon catheter may be used for patients who have difficulty maintaining subcutaneous sites)
- standard intravenous giving set
- alcohol swab
- clear occlusive dressing
- disposable gloves (one pair)
- prescribed solution for infusion (available on GP10 prescription)
- drip stand
- infusion chart
- prescription chart.
Nitrous oxide 50%/oxygen 50% gas mixture

Nitrous oxide is a colourless, odourless and tasteless gas. It has a quick onset of action of two to three minutes due to rapid diffusion across cell membranes and a rapid elimination via the lungs when inhalation stops. Nitrous oxide is traditionally used for the maintenance of anaesthesia in concentrations of 70%. When inhaled in concentrations lower than this, but above 25% it produces profound and powerful analgesia without loss of consciousness1. Nitrous oxide 50% and oxygen 50% (Entonox®, Equanox®) is available in a gas cylinder for use as an analgesic.

Administration is self regulated by the use of a face mask or mouthpiece connected through a demand valve to the cylinder. The demand valve is operated by the act of inhalation and closes down when the patient stops inhaling2. The face mask/mouthpiece is held in place by the patient. Therefore in overdose, if light anaesthesia occurs, the mask will fall away.

Three cylinders sizes (0.5m³, 2.0m³ and 5.0m³) are available on GP10 prescription. However the cylinder head including the demand valve is not. Arrangements for availability of equipment in primary care vary locally and may include loan of the nitrous oxide/oxygen cylinder head and demand valve from a local hospice.

Indications for nitrous oxide/oxygen in palliative care include:

- painful procedures; for example, during painful dressing changes or manual bowel evacuation3-5
- spontaneous spasmodic pain; for example, bladder spasms and spasms of pain related to bone metastases or nerve injury5.

The use of nitrous oxide/oxygen in the latter situation is particularly beneficial as these pains are usually of short duration. The use of a breakthrough dose of an opioid can render the patient drowsy due to the opioids longer duration of action compared with nitrous oxide/oxygen.

Side-effects of nitrous oxide/oxygen include light-headedness, dry mouth and drowsiness and are quickly reversed on discontinuation of the nitrous oxide/oxygen. Rarer side-effects reported include nausea, amnesia, headache and numbness5. Long-term use of nitrous oxide/oxygen (over days or weeks) can result in inactivation of vitamin B12 with the resultant reduction in folate metabolism and pernicious anaemia. Full blood count should be monitored for megaloblastic anaemia and leucopenia if nitrous oxide/oxygen is used for more than 24 hours and when administration is more frequent than every four days2. Long-term use is also associated with bowel distension, middle ear damage and rupture of ear drums.

Contra-indications to nitrous oxide/oxygen include presence of pneumothorax, bowel obstruction with abdominal distension, severe chronic obstructive airways disease and impaired levels of consciousness2,4,5. In some situations the patient’s condition may dictate whether nitrous oxide/oxygen can be considered; for example, a patient with generalised weakness may not be able to self administer the gas.
Handling requirements necessitate that nitrous oxide/oxygen is stored above 10°C for at least 24 hours before use. Below –6°C nitrous oxide separates out from oxygen.

**Heliox**

Heliox is a medical gas which is used in the treatment of stridor. Heliox is a mixture of helium 79% and oxygen 21% and is less dense and viscous than normal air. It helps to reduce the respiratory work required to overcome upper airways obstruction. It is only used as a temporary measure to provide the patient with oxygen.

**Fentanyl transdermal patches**

Fentanyl is an opioid receptor agonist formulated in a transdermal patch delivery system. Fentanyl is considered an alternative opioid in moderate to severe opioid responsive pain in patient who are unable to tolerate morphine side-effects. There are two different formulations of fentanyl patches:

- a reservoir patch, where the drug is contained within a reservoir, and a rate-limiting membrane controls delivery of the drug
- a matrix patch with the medicine distributed through an adhesive drug matrix.

The two formulations of patches, and different brands, vary in appearance and to avoid patient confusion, patients should not be switched between brands without explanation.

These are available in five patch sizes (12 micrograms/hour, 25 micrograms/hour, 50micrograms/hour, 75 micrograms/hours, 100 micrograms/hour). The 12 microgram/hour patch (matrix formulation) is only licensed for escalation between doses and is not licensed as a starting dose for titration. Several patches can be applied at one time to provide the required dose, although in practice the maximum dose administered is usually 300 micrograms/hour (three 100 micrograms/hour patches).

Whilst morphine remains the opioid of choice for moderate to severe pain, transdermal fentanyl may be used when the patient’s pain is stable, they require an opioid for moderate to severe pain and:

- oral route is unavailable (e.g. persistent nausea and vomiting, bowel obstruction, difficulty or pain when swallowing) or
- patient has unacceptable side-effects from morphine or
- patient has severe and persistent constipation with morphine despite prophylactic laxative treatment.
Transdermal fentanyl should not be used in patients with:
- unstable pain
- fever beyond 39°C (increased absorption of fentanyl)
- poor skin condition (e.g. area irradiated in last four weeks, oedematous, extensive scarring).

Initiating transdermal fentanyl
- Patients should be on a stable dose of strong opioid before fentanyl patch is initiated.
- Calculate the dose of fentanyl from the conversion chart (refer to manufacturer’s literature).
- Ensure that the first 12 hours after patch application is covered with another opioid, due to the lag time of 6-12 hours to onset of action (e.g. apply fentanyl patch at the same time as last dose of morphine sulphate modified release tablet).
- A short-acting opioid (morphine sulphate immediate release tablets or liquid, diamorphine SC bolus injection) should be available for breakthrough pain.
- 10% of patients changing from morphine to fentanyl will experience withdrawal symptoms in the 24 hours after switch (diarrhoea, abdominal pain, flu-like symptoms). Giving breakthrough doses of morphine can counteract this.
- The laxative dose may need to be reduced as transdermal fentanyl can be less constipating than morphine.

Adjusting transdermal fentanyl
- Review the transdermal fentanyl dose after 48-72 hours.
- Assuming the pain is opioid-responsive, titrate the dose of transdermal fentanyl in 12 or 25 microgram/hr increments.

NB: increases in dose take 36-48 hours before steady state drug levels are reached.

Discontinuing transdermal fentanyl
Discontinuation of transdermal fentanyl has to be done with care, as a depot of drug remains under the skin for several days following removal of the patch. Patients should be monitored carefully for signs of opioid toxicity for 24-48 hours if transdermal fentanyl is being changed to another opioid. The patient’s clinical condition should dictate the approach for removal of transdermal fentanyl and initiation of another opioid. Most specialist palliative care teams do not discontinue this treatment when a patient has unstable pain and is close to death, due to the difficulty of maintaining analgesia during the switch-over period. Instead these units leave the patch in situ, whilst changing every 72 hours and add in a subcutaneous continuous infusion of diamorphine/morphine if additional analgesia is required. Detailed guidance on the use of transdermal fentanyl is available in the Lothian Palliative Care Guidelines at www.palliativecareguidelines.scot.nhs.uk
Counselling points
Patients should be counselled regarding how to apply the transdermal fentanyl correctly. In addition, the following information may be useful:

- confirm type of patch is as expected (reservoir or matrix)
- change the patch at the same time of day every three days
- hair can be clipped, not shaved
- apply to a different skin site after removal of previous patch
- do not use irradiated or irritated skin areas, scar tissue or oedematous skin
- avoid direct contact with heat such as electric blankets and hot water bottles
- if adherence is poor, use micropore tape or an adhesive dressing. It is important to ensure that proper contact of the patch to the skin occurs and if adhesion is poor, reconsideration of the suitability of the patch is required
- used patches should be folded over and disposed of in the normal household waste.

Spinal medicine administration
Spinal medicine administration is an interventional technique considered for patients whose pain is not relieved by standard approaches. One study has estimated that 1% of patients will benefit from an epidural in cancer pain management.¹

Indications for spinal analgesia:
- pain not adequately controlled
- oral or parenteral strong opioids, for morphine responsive pain, are ineffective
- systemic opioids have caused intolerable side-effects
- adjuvant analgesics are ineffective
- other therapeutic alternatives ineffective or not applicable.

The spinal route of administration involves all routes of administration near to, or within, the spinal meninges. The epidural and intrathecal routes are used most frequently. The epidural route is immediately outside the dura mater, within the vertebral spinal canal and the intrathecal route is inside the thecal sac or dura mater.²

Skilled personnel are required to insert epidural and intrathecal systems, and monitoring afterwards is essential. Strict aseptic precautions must be maintained at insertion and in any manipulation of the catheter thereafter (e.g. changing of drug reservoir, or bolus dosing). The procedure should ideally be done in a hospital setting.

The prognosis of the patient may dictate the permanency of the type of catheter placement. Percutaneous catheters are used for short term use. The catheter is fixed by secure taping or subcutaneous tunnelling. With this system, the infusion is often delivered via a syringe driver or small infusion device enabling the patient to be ambulant and, in some situations, cared for at
home. Training of the primary care team and access to support is essential. For patients with a longer prognosis, fully implantable intrathecal systems can be used.

Infusion devices
Various administration devices have been used both in hospital and home settings and include syringe drivers, electronic ambulatory pumps and disposable self regulating pumps. Devices suitable for home use must be simple to use and tamper-proof.

Medicines commonly administered via the spinal route
Medicines administered by the spinal route include:
- opioids (morphine, diamorphine, fentanyl)
- local anaesthetics (bupivacaine)
- clonidine.

NB: preservative free products must always be used to prevent neurotoxicity.

Various equianalgesic doses for systemic morphine and epidural morphine have been reported, making the calculation of an appropriate starting dose important. The starting dose can depend on dose and route of administration of the opioid the patient is currently receiving, intended route of administration (e.g. epidural or intrathecal) and the clinical status of the patient. Pain assessment should be carried out regularly and the degree of analgesia as well as side-effects monitored to facilitate titration of dose. It is important to note opioids administered via the epidural or intrathecal route are very potent. Epidural morphine is 10 times more potent than subcutaneous morphine and intrathecal morphine is 100 times more potent than subcutaneous morphine. Due to the lipophilicity and hydrophilicity of different opioids the normal dose equivalencies which would normally be used for subcutaneous or oral administration do not apply to spinal administration. Advice on spinal opioid switching should always be obtained from a specialist with experience of spinal analgesia. This is due to the direct action of the opioid on opioid receptors in the dorsal horn.

Spinal infusions should ideally be prepared under aseptic conditions in a hospital pharmacy department, or commercially prepared infusions used.

Complications
The common adverse effects of spinal opioids are more routinely seen in the acute pain setting (e.g. post operative or obstetric). These include pruritis, nausea and vomiting and respiratory depression. In the palliative care population, patients are unlikely to be opioid naive and therefore are not likely to experience these side-effects.

Infection including catheter sepsis and mechanical failure of the pump are not uncommon in the palliative care patient. Catheters can migrate out of the subarachnoid or epidural space necessitating resiting. Long term placement of epidural catheters can result in epidural fibrosis, reducing the effectiveness of the flow of medicine into the epidural space.

NB: Enteral administration is covered in Chapter 7.
Activity 1

For each medicine delivery system, obtain the following information:

- equipment and accompanying accessories necessary to use the equipment
- availability of equipment and accessories on the drug tariff
- where they are supplied from
- who maintains them
- patient/carer counselling points regarding use and maintenance of medicine delivery system.

1. Syringe drivers/pumps

2. Nebulisers and medical gases
3. Nitrous oxide 50%/oxygen 50% gas mixture

4. Subcutaneous hydration
Activity 2

1. Mr X has been taking morphine sulphate modified release tablets 60mg bd for pain relief. His pain is controlled, but he is now unable to take medicines orally and the decision has been made to change to a continuous subcutaneous infusion.

What medicine and dose of analgesic should be prescribed for the continuous subcutaneous infusion via a syringe driver/pump and what dose should be prescribed for breakthrough pain?

2. Miss Y had been taking co-codamol 30/500 two tablets four times daily for pain relief and is currently pain free. She is currently experiencing dysphagia and the doctor has decided to use a syringe driver/pump.

What dose of diamorphine should be prescribed for this patient?

3. Mr Z is a 71 year old man with lung cancer and raised intracranial pressure. His condition is deteriorating and the doctor has decided to change him from oral therapy to a subcutaneous infusion via a syringe driver/pump.

Current medicine therapy is:
- morphine sulphate modified release tablets 30mg bd
- morphine sulphate immediate release liquid 10mg prn for breakthrough pain (requiring three breakthrough doses per day)
- dexamethasone 4mg daily
- cyclazine 50mg tablets three times daily
- co-danthrusate capsules.

What recommendations would you make regarding his current medication for administration via a syringe driver/pump?
Suggested answers

Activity 2
1. Mr X has been taking morphine sulphate modified release tablets 60mg bd for pain relief. His pain is controlled, but he is now unable to take medicines orally and the decision has been made to change to a continuous subcutaneous infusion.

What medicine and dose of analgesic should be prescribed for the continuous subcutaneous infusion via a syringe driver/pump and what dose should be prescribed for breakthrough pain?

*Morphine 3mg oral is equivalent to 1mg of diamorphine subcutaneously.*

**Total morphine dose over 24 hours = 120mg.**
**diamorphine over 24 hours = 120/3.**
**= 40mg/24 hours.**

*Breakthrough should be one sixth of the total daily dose.*
**diamorphine 40/6 = approx. 5 to 7mg diamorphine subcutaneously prn.**

2. Miss Y had been taking co-codamol 30/500 two tablets four times daily for pain relief and is currently pain free. She is currently experiencing dysphagia and the doctor has decided to use a syringe driver/pump.

What dose of diamorphine should be prescribed for this patient?

*Codeine is approximately 1/10th (one tenth) as potent as oral morphine.*

**Total codeine dose over 24 hours = 240mg.**
**Equivalent dose of oral morphine would therefore be 24mg over 24 hours.**

**diamorphine over 24 hours = 24/3.**
**= 8mg over 24 hours.**

*Miss Y should be commenced on diamorphine 5-10mg/24 hours.*

*Breakthrough dose is one sixth of the total daily dose e.g. Diamorphine 1-2mg.*
3. Mr Z is a 71 year old man with lung cancer and raised intracranial pressure. His condition is deteriorating and the doctor has decided to change him from oral therapy to a subcutaneous infusion via a syringe driver/pump.

What recommendations would you make regarding his current medication for administration via a syringe driver/pump?

*Morphine 3mg oral is equivalent to 1mg of diamorphine subcutaneously.
Total dose of morphine over 24 hours = 60mg + 30mg (from breakthrough doses).
= 90mg.
*Diamorphine dose should be 30mg/24 hours.
Breakthrough dose should be 1/6th of the 24 hour diamorphine dose and therefore should be diamorphine 5mg when required for breakthrough pain.
*Cyclizine 150mg/24 hours is compatible with diamorphine (at doses suggested) and should be combined with diamorphine in the syringe driver/pump. Water for injection should be used as a diluent. Dexamethasone should be given once or twice daily as a SC injection. It has a long biological duration of action therefore doses not need to be administered continuously.*
References

Syringe drivers/pumps

1 Cousins DH, Upton DR. Medication Errors. Make infusion pumps safer to use. Pharmacy in Practice 1995;5:401-406


Nebulisers and medical gases

1 BTS guidelines on current best practice for nebuliser treatment. Thorax 1997;52(supplement 2):S1-S43

2 Ahmedzai S, Davis C. Nebulised drugs in palliative care. Thorax 1997;52 (supplement 2):S75-S77

Subcutaneous hydration


Nitrous oxide 50%/oxygen 50% gas mixture
1 BNF (current issue).
2 Equanox (50% oxygen balance nitrous oxide). Summary of Product Characteristics. Linde Gas UK Ltd.

Fentanyl transdermal patches

Spinal medicine administration
Glossary
Glossary

**Acupuncture**
A system where insertion of special needles in particular parts of the body is used for the production of anaesthesia, pain relief and treatment of certain conditions.

**Angular chelitis**
Chronic sores in the corners of the mouth caused by a variety of factors including candidosis, Vitamin B12 deficiency, iron deficiency.

**Anteromedial**
Middle front region.

**Asthenia**
Want of strength.

**Cachexia**
Severe wasting. Highest incidence in gastrointestinal and bronchogenic carcinomas.

**Gastric stasis**
Reduction in the movement of gastric contents.

**Catabolism**
Chemical breakdown of complex substances in the body to form simpler ones, with the release of energy.

**Cerebral anoxia**
Lack of oxygen to cerebral area of brain.

**CRP**
C-reactive protein.

**Cytokines**
Endogenously produced protein.

**Desquamation**
Peeling of superficial layer of the skin.

**Dura mater**
Strong fibrous membrane forming the outer covering of the brain and spinal cord. It lines the inner surface of the protecting bones.

**Dysphagia**
Difficulty in swallowing.

**Dyspnoea**
Difficult or laboured breathing.

**Enterocolic fistula**
An abnormal passage connecting small intestine and colon.

**Gastrectomy**
Excision of part or whole of the stomach.

**Gluconeogenesis**
Production of glucose from amino acids in the liver.

**Hypercalcaemia**
Excess of calcium in blood which, if left untreated, can lead to confusion, drowsiness and coma. More common in carcinoma of bronchus, breast and myeloma.

**Hypodermoclysis**
Subcutaneous administration of fluids.

**Ileostomy**
An operation to make an opening through the abdominal wall into the ileum so that intestinal contents can be evacuated, bypassing the colon.

**Interstitial space**
Situated within the tissue spaces or between tissues.

**Intrathecal route**
Route of delivery directly into the spinal cord, usually into the subarachnoid space.
JVP
Jugular venous pressure

Lipolysis
Enzymatic breakdown of fats.

Medulla oblongata
Portion of the spinal cord which is contained inside the cranium.

Mucositis
Inflammation of the mucous membranes.

Myenteric plexus
Aggregation of nerves in myenteric region, controlling GI motility.

Myoclonus
Brief, twitching muscular contraction.

Neutropenia
Fall in the number of neutrophils in the blood below a normal level.

NMDA receptor
M-methyl D-aspartate receptor-channel complex found in the dorsal horn of the spinal cord.

Paraesthesia
Abnormal tingling sensation (‘pins and needles’).

Pharyngeal irritation
Irritation of the pharynx.

Pleural drain
Drainage of fluid from between the membrane lining the lung tissue (visceral pleura) and the overlying membrane lining the chest wall (parietal pleura).

Pleural effusion
Collection of fluid in the space between the visceral and parietal pleura.

Pleurodesis
Instillation of agent into the pleural space in order to prevent recurrence of pleural effusion.

Rhinorrhea
Excessive discharge of mucous from the nose.

Stomatitis
Diffuse inflammatory, erosive and ulcerative conditions affecting the mucous membranes lining the mouth.

Tachypnoea
Unusually rapid breathing.

TENS
Transcutaneous Electrical Nerve Stimulation used in a variety of clinical pain conditions.

WCC
White cell count.

Xerostomia
Dryness of the mouth due to lack of saliva.
Multiple choice questionnaire and answer sheet
Congratulations

You have now made it to the end of the pack.

However, we require one more task of you – to complete the attached self-assessment questionnaire. This allows you to test your understanding of the package and to receive feedback on the answers.

Tick each answer as true or false.

Detach the answer sheet on the last page along the perforation and copy your choices onto this sheet. We would also really appreciate any of your comments about all aspects of the pack. Your comments allow us to improve future distance learning packages. Once completed with your name and address details, return it to:

NHS Education for Scotland (Pharmacy)
3rd floor, 2 Central Quay
89 Hydepark Street
Glasgow G3 8BW

Alternatively, you may wish to complete the multiple choice questions online at the NES Pharmacy website at www.nes.scot.nhs.uk/pharmacy/MCQtesting/

You will receive an instant score if you choose this method!

If you are not resident in Scotland, you should return your completed multiple choice questionnaire to the appropriate centre for pharmaceutical postgraduate education.

Please note there is no negative marking, so do attempt all the questions by ticking the appropriate true/false box.
Multiple choice questionnaire

- Please answer the following questions by ticking the appropriate box.
- Transfer your answers on to the enclosed answer sheet at the back and return it in the envelope provided for marking.
- You will then receive a record of completion showing the number of study hours this represents.

Difficult to control pain

1. Consider these statements on opioid toxicity and adjuvant analgesics:
   a) If a patient experiences hallucinations with morphine, then all other opioids for moderate to severe pain will also cause hallucinations.
      true □   false □
   b) Parenteral administration of fluid should be attempted in a patient who is opioid toxic, if the oral route is unavailable.
      true □   false □
   c) Amitriptyline treatment for neuropathic pain takes four to six weeks to be effective.
      true □   false □
   d) Oromucosal cannabinoid spray (Sativex) is useful for neuropathic pain in multiple sclerosis.
      true □   false □

2. The following statements regarding breakthrough pain are correct:
   a) The dose of breakthrough analgesia is usually one quarter of the daily dose of maintenance opioid.
      true □   false □
   b) Patient requiring more than two doses of breakthrough analgesia in 24 hours should have their dose of maintenance opioid increased by 30–50%.
      true □   false □
   c) All breakthrough pain can be anticipated.
      true □   false □
   d) Patients may confuse treatments for maintenance analgesia and breakthrough analgesia.
      true □   false □
**Nausea and vomiting**

3. The following statements about nausea and vomiting are correct:

a) Hypercalcaemia is an irreversible cause of nausea and vomiting.  
   true □ false □

b) Dexamethasone, at an initial dose of 2-4mg is the treatment of choice for nausea and vomiting induced by raised intracranial pressure?  
   true □ false □

c) Both constipation and anxiety can contribute to nausea and vomiting.  
   true □ false □

d) Levomepromazine blocks several different receptors in various emetic pathways and is therefore a broad-spectrum anti-emetic.  
   true □ false □

4. A patient with cervical cancer has developed projectile vomiting. She becomes nauseous each day after her evening meal and vomits large volumes several hours later. She is also complaining of colicky abdominal pain. Complete intestinal obstruction is diagnosed.

a) She should have all her medicine therapy delivered via a non-oral route until the nausea and vomiting are controlled  
   true □ false □

b) Metoclopramide 30mg given subcutaneously will improve her symptoms.  
   true □ false □

c) Octreotide would be useful in reducing the volume of vomit.  
   true □ false □

d) More than one medicine may be required to control her nausea and vomiting.  
   true □ false □

**Other Gastro-intestinal diseases**

5. A patient develops diarrhoea after a period of 8 days when her bowels have not opened

a) Loperamide should be used to treat the patient  
   true □ false □

b) The patient may develop other symptoms due to her bowel problems including confusion, abdominal pain, loss of appetite.  
   true □ false □

c) These symptoms may be due to the use of morphine sulphate for pain relief.  
   true □ false □

d) Treatment may include the use of rectal laxatives.  
   true □ false □
6. The following statements are true:

a) 5HT3 antagonists do not cause constipation.
   true □  false □

b) It is preferable to treat patients prophylactically with laxatives when they are prescribed drugs known to cause constipation.
   true □  false □

c) Faecal impaction may lead to patients experiencing urinary incontinence.
   true □  false □

d) Rectal measures to relieve constipation should be used routinely in patients with cancer.
   true □  false □

**Dyspnoea**

7. Which of the following treatments can be used to relieve dyspnoea

a) Corticosteroids.
   true □  false □

b) Chest drain.
   true □  false □

c) Heliox.
   true □  false □

d) Anticoagulation.
   true □  false □

8. The following statements regarding dyspnoea in palliative care are correct?

a) For patients who are currently on an opioid for pain who are experiencing dyspnoea it is appropriate to increase their dose by 50-75%.
   true □  false □

b) Palliative care patients who experience dyspnoea may describe the feeling as being smothered.
   true □  false □

c) Education of the opioids to use and how and when to take them for dyspnoea is very important for the patient or their families.
   true □  false □

d) Chemotherapy can be offered to some patients in an attempt to reduce tumour bulk which may reduce breathlessness.
   true □  false □
Nutrition

9. The following statements about cachexia are correct:
   a) Corticosteroids are effective in the longterm treatment of anorexia.  
   b) Megestrol acetate is effective in the longterm treatment of anorexia.
   c) Megestrol acetate is a safe and effective treatment of cachexia in a patient with congestive heart failure.
   d) Corticosteroids improve nutritional status.

10. The following statements are true:
   a) All oral medicines are licensed to be administered via a PEG tube.
   b) Medicines can be added to enteral feeds to permit administration without problems.
   c) Using the correct flushing techniques avoids enteral tubes blocking.
   d) Carers often measure a patient’s wellbeing by the nutritional intake.

Mouth and skin care

11. A patient has developed xerostomia:
   a) This may explain the burning sensation in her mouth.
   b) It would be appropriate to treat this symptom with lemon and glycerine mouthwash.
   c) She is at high risk of developing oral candidiasis and angular cheilitis.
   d) She should be advised to sip plain cold water frequently as this is as effective as artificial saliva.
Neurological complications

12. Which of the following should be considered prior to commencing an antidepressant?

a) Is there a potential for seizure activity (e.g. brain metastases)?  
   - true □  false □

b) Concurrent therapy particularly other antidepressants used for a different indication.  
   - true □  false □

c) Concurrent hyponatraemia.  
   - true □  false □

d) Patient compliance poor and likely to discontinue therapy suddenly.  
   - true □  false □

13. The following statements about agitation are false?

a) Agitation can be an acute problem which can be managed by firstly assessing the cause and then removing the cause.  
   - true □  false □

b) A diary may be useful to document trigger factors for anxiety/agitation.  
   - true □  false □

c) Optimal surroundings including appropriate light, reassurance and continuity of surroundings can help.  
   - true □  false □

d) Non pharmacological interventions are never successful in treating agitation.  
   - true □  false □

Last days of life

14. Mr G has advanced prostate cancer, angina and hypercholesterolaemia. He has become increasingly weak over the previous 48 hours. His level of consciousness is fluctuating and he is eating and drinking little. Previously his main symptom was pain which had been controlled by oral analgesics.

a) All his medication must be changed over immediately to be delivered by non-oral routes.  
   - true □  false □

b) His analgesic dose must be increased as a matter of course as he has deteriorated.  
   - true □  false □

c) Both his antianginal and lipid lowering therapy must be continued up until his death.  
   - true □  false □

d) It is inappropriate to give Mr G artificial nutrition, but it may be appropriate to provide parenteral hydration to prevent dehydration.  
   - true □  false □
15. In the last days of life, agitation can be caused by:

a) Constipation. [true] [false]

b) Uncontrolled pain. [true] [false]

c) A drug withdrawal syndrome, if antiemetics are stopped suddenly. [true] [false]

d) Opioid accumulation due to dehydration. [true] [false]

16. In the last days of life, palliative care services for patients:

a) Out of hours are consistent and easily accessed. [true] [false]

b) Enable most patients who have stated a preference to die at home to do so. [true] [false]

c) Are provided regardless of disease. [true] [false]

d) Can be well co-ordinated with the assistance of initiatives such as the Gold Standards Framework and the Liverpool Care Pathway for the Dying Patient. [true] [false]

**Medicine Delivery Systems**

17. When setting up a syringe driver/pump:

a) They should never be sited over an area of lymphoedema. [true] [false]

b) They should be considered for all patients who are referred to palliative care. [true] [false]

c) The catheter may be left in for 72 hours or longer provided there is no redness or inflammation at the site. [true] [false]

d) The catheter should not be placed near a joint as this would be uncomfortable for the patient. [true] [false]
18. Which of the following is an off-label use of a medicine:

a) Morphine via subcutaneous route.  
   true □ false □

b) Amitriptyline for neuropathic pain.  
   true □ false □

c) Diamorphine via subcutaneous route.  
   true □ false □

d) Clonidine for sweating.  
   true □ false □

19. A Fentanyl 50 microgram/hour patch is considered equivalent to:

a) 45mg twice daily MST  
   true □ false □

b) 90mg twice daily MST  
   true □ false □

c) 135mg twice daily MST  
   true □ false □

d) 180mg twice daily MST  
   true □ false □

20. Which of the following medicines cannot be given via a nebuliser?

a) Heliox.  
   true □ false □

b) Midazolam.  
   true □ false □

c) Salbutamol.  
   true □ false □

d) Local anaesthetics.  
   true □ false □
Multiple choice questionnaire  

Answer sheet

The pharmacist in palliative care

1  a □  2  a □  3  a □  4  a □  
   b □  b □  b □  b □  
   c □  c □  c □  c □  
   d □  d □  d □  d □  

5  a □  6  a □  7  a □  8  a □  
   b □  b □  b □  b □  
   c □  c □  c □  c □  
   d □  d □  d □  d □  

9  a □  10  a □  11  a □  12  a □  
   b □  b □  b □  b □  
   c □  c □  c □  c □  
   d □  d □  d □  d □  

13 a □  14 a □  15 a □  16 a □  
   b □  b □  b □  b □  
   c □  c □  c □  c □  
   d □  d □  d □  d □  

17 a □  18 a □  19 a □  20 a □  
   b □  b □  b □  b □  
   c □  c □  c □  c □  
   d □  d □  d □  d □  

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Comments