Clinical Practice Guideline for Palliative Care

NOTE:

It has been 5 years since the publication of this Clinical Practice Guideline and it is subject to updating.

The recommendations included should be considered with caution taking into account that it is pending evaluate its validity.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH AND CONSUMER AFFAIRS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO

Plan de Calidad para el Sistema Nacional de Salud

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SANIDAD

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Presentation

Care practice is becoming more and more complicated due to many different factors. One of the most relevant factors is the exponential increase of scientific information.

To make clinical decisions that are adequate, safe and effective, practitioners need to devote a lot of effort in continously updating their knowledge.

In 2003, the Interterritorial Council of the Spanish NHS created the GuiaSalud Project whose final aim is to improve clinical decision-making based on scientific evidence, via training activities and the configuration of a registry of Clinical Practice Guidelines (CPG). Since then, the GuiaSalud project has assessed dozens of CPGs in agreement with explicit criteria stipulated by its scientific committee. It has registered them and has disseminated them over the Internet.

At the beginning of 2006, the D.G. of the Quality Agency of the National Health System prepared the Quality Plan for the National Health System, which was divided into in 12 strategies.

The purpose of this Plan is to increase the cohesion of the National Health System and help guarantee maximum quality health care for all citizens regardless of their place of residence.

As part of the Plan, different agencies and expert groups in prevalent pathologies related to health strategies were entrusted with the preparation of eight CPGs. This Palliative Care guideline is the fruit of this assignment.

The definition of a common methodology to prepare the CPG for the NHS was also requested and this has been prepared as a collective effort of consensus and coordination among the Spanish CPG expert groups. This methodology was used as the basis to prepare this Palliative Care guideline and the other CPGs driven by the Quality Plan.

The GuiaSalud Project was renewed in 2007 and the Clinical Practice Guideline Library was created. This project developed into the preparation of the CPGs and included other Evidence-Based Medicine services and products. It also aims to favour the implementation and assessment of the use of CPGs in the National Health System.

This CPG deals with palliative care (PC) and it is the result of the work of a large group of expert professionals from different Autonomous Communities, who represent all the professions involved in PC. The scientific societies involved have collaborated in the review process of the guideline. An attempt has also been made to incorporate the viewpoint of patients and carers via qualitative research techniques.

Although the evidence on the effectiveness of the measures aimed at dealing with palliative care problems may be scarce, the evidence synthesised in the CPG is a tool to improve the care and act as support to the initiatives on the improvement in the organisation of the PC.

The CPG proposes planned and organised care that guarantees integral, quality and coordinated care for people in palliative care.

We are convinced that its use will contribute to an improvement of the quality of the care given to the people that need it and to their families.

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Spanish Society for Palliative Care (SECPAL)

Spanish Society of Primary health care Pharmacists (SEFAP)

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Spanish Society of Home Hospitalisation

Spanish Society of Family and Community Medicine (SEMFYC)

Spanish Society of Intensive and Critical Medicine and Coronary Units (SEMICYUC)

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Members of these societies have participated in the authorship and expert collaboration for the CPG

Declaration of interests

A declaration of interests has been requested from all the members of the Working Group, as well as from professionals who have participated as expert collaborators (appendix 9).

Questions to be answered

Introduction to palliative care

1. What is the validity of the prognosis scales to predict survival in patients in EOL?

Information, communication and decision-making

2. How should the team attending to the patient and his or her family communicate?
3. What must the communication training of the health professional working with patients in EOL be like?
4. What legal regulations and ethical principles exist relating to the communication with the person in EOL and with his or her family in our setting?
5. What are the decision-making elements in EOL?

Symptom Control

6. What is the prevalence of the different symptoms in patients in EOL?
7. How valid are the scales that evaluate the intensity of symptoms in patients in EOL?
8. How should drugs be used in palliative care?

Pain treatment

9. What is the prevalence of pain in EOL?
10. How valid are the different scales for assessing pain?
11. How efficient are the different analgesics (simple analgesics, NSAID, combinations of the above, opioids, etc.) and of adjuvant drugs in pain?
12. How effective are the different opioids for breakthrough pain?
13. What is the analgesic effectiveness of radiation therapy, palliative chemotherapy, bisphosphonates and calcitonin in cancer patients with bone metastasis?
14. How effective are drugs in treating neuropathic pain of people in EOL?

Asthenia, anorexia-cachexia and dehydration

15. What is the most suitable treatment for asthenia in people in EOL?
16. What is the most suitable treatment for anorexia-cachexia in people in EOL?
17. What is the most suitable treatment for dehydration in people in EOL?

Breathing symptoms

18. How effective are opioids and adjuvant treatments when treating dyspnoea?

19. How effective is oxygen when treating dyspnoea?

20. What is the most suitable treatment for coughing in people in EOL?

21. What is the most suitable treatment for obstruction of the superior vena cava?

Psychological and psychiatric symptoms

22. What is the most suitable treatment for delirium in people in EOL?

23. What is the most suitable treatment for insomnia in people in EOL?

24. What is the most suitable treatment for anxiety in people in EOL?

25. What is the most suitable treatment for depression in people in EOL?

Digestive symptoms

26. What are the most suitable measures for preventing and treating mucositis in people in EOL?

27. What is the most suitable treatment for dry mouth?

28. What are the most suitable measures for preventing and treatment oral candidiasis?

29. What is the most suitable treatment for dysphagia?

30. What is the most suitable treatment for nausea and vomiting?

31. What is the most suitable treatment for constipation?

32. What is the most suitable treatment for diarrhoea?

33. What is the most suitable treatment for bowel obstruction?

34. What is the most suitable treatment for ascites?

35. What is the most suitable treatment for hiccups?

Skin care

36. What is the best way to prevent ulcers in people in EOL?

37. What is the most suitable treatment for ulcers in people in EOL?

38. What is the most suitable treatment for fungating wounds?

39. What is the most suitable treatment for pruritus?

Urinary symptoms

40. What is the most suitable treatment for urinary urgency?

Emergencies

41. What is the most suitable treatment for hypercalcaemia in people in EOL?

42. What is the most suitable treatment for spinal cord compression in people in EOL?

43. What is the most suitable treatment for seizures in people in EOL?

45. What is the most suitable treatment for bledding in people in EOL?

Psychosocial and spiritual support to people in EOL

45. How to identify the psychosocial needs of people in EOL?

46. How best to attend to the psychosocial needs?

47. How are the spiritual needs identified?

48. How do the spiritual needs influence the evolution of people in EOL?

49. What is the most suitable strategy to attend to the spiritual needs of people in EOL?

Psychosocial support to the family

50. How are the family's psychosocial support needs identified?

51. What is the best way to attend to the psychosocial and support needs of the family?

52. What are the risk factors of family exhaustion syndrome?

Care during the final days. Agony

53. What kind of care must be given to patients and their families during the final days of life?

54. What is the most suitable treatment for the death rattle of the dying person?

Palliative sedation

55. What are the indications to carry out palliative sedation?

56. What must the decision-making process be like in palliative sedation?

57. What drugs and administration methods are recommended for palliative sedation?

Bereavement

58. What is the definition of normal bereavement and what are the phases and signs?

59. What is the definition of complicated bereavement and what are the signs?

60. What are the risk factors for complicated bereavement and how are they assessed?

61. How effective are interventions in normal bereavement, risk bereavement and complicated bereavement?

Summary of recommendations

Introduction to palliative care

Organisational aspects of palliative care

D	Palliative interventions should be based on the patient's and the family's needs more than on expected survival time.
D	All patients in EOL should have access to a basic level of care in all care areas.
B	Health organisations should foster the training of their professionals to provide basic PC, regardless of the care area.
D	Service organisations should guarantee accessibility to specialised care when necessary.
B	PC at any level should preferably be provided by a suitable multi-disciplinary team.
B	Health organisations should define the functions they have to carry out and the training that the different service procurement levels should have in PC with respect to patients and their families.
B	Health organisations and the actual care services should guarantee coordination among the different services and care areas as well as continuity of care, 24 hours a day, 365 days a year.

Survival prediction

C	To estimate survival in patients with advanced cancer, elements other than clinical impression, should be taken into account, such as the presence of prognostic factors, the functional status (Karnofski) or the PaP prognostic scale (Palliative Prognostic Score). The latter is recommended within the context of specialised PC units or in oncology, as it has not been validated in other areas.
C	In non-cancer patients, the general survival predictive models require further validation. It is preferable to consider bad prognosis factors of each disease or validated scales (Seattle Heart Failure Model for ICC and MODEL for hepatic failure), always bearing uncertainty in mind and the less predictable trajectory of non-malignant diseases.
√	The way in which the prognosis is notified is just as important as its precision.
√	Validation of the different instruments in our setting is necessary, as well as the assessment of the impact of their use on clinical practice.

Information, communication and decision-making

C	Health professionals should have the necessary skills to effectively communicate with patients and carers and should receive adequate training in this regard.
√	The information and communication should be based on the preferences expressed by the patients. Health professionals should avoid interpreting their desires.
D	It is important for health professionals to explicitly show their willingness to listen and inform.
B	Patients' needs for information and preferences must be evaluated on a regular basis.
D	Relevant news, such as the diagnosis, should not be delayed and each patient's desire for information must be respected individually (including the wish to not be informed). They should be informed sincerely, sensitively and with realistic hope. This type of information must be provided in a quiet, comfortable place, with privacy and without interruptions.
B	Verbal information can be accompanied by other reinforcement information methods such as written information. The methods should be based on individual preferences.
B	Health organisations should give professionals working with patients who require PC the possibility of receiving suitable training in communication skills. The training should be intensive, based on real scenarios and with subsequent refresher sessions.
D	The participation of patients and carers in decision-making at the end of life should be fostered, through suitably trained professionals and respecting people's wishes not to take part in the decisions.
D	Professionals who participate in decision-making must provide clear and sufficient information, letting the patient and his or her relations express their doubts and fears, solving their questions and providing the necessary time for reflection.
D	Clinics should make decision-making easy when faced with ethical dilemmas in EOL (limitation of therapeutic effort, food and hydration, sedation, etc.) bearing in mind the values and preferences of the patient and his or her family.
D	If the patient is not able to make decisions, the following options should be considered, in the order in which they are presented: a) Preliminary guidelines, if any. b) Desires expressed by the patient and included in his or her clinical records, if any. c) Legal representative. d) Closest relations in charge.
D	It is advisable to inform the team of the decisions adopted and record the process in the clinical records.
D	If there are doubts during the decision-making process, a request for advice from experts may be indicated (other professionals, Healthcare Ethics Committee, etc.).

Symptom Control

General principles for symptom control

D	The evaluation of symptoms of the EOL patient must be multidisciplinary, individualised, adapted to the patient and his or her family and continued in time.
D	If the use of symptom evaluation scales is chosen, the use of validated instruments is recommended. The ESAS scale can be used in our setting. The Rotterdam Symptom Checklist scale (validated in Spanish language) can be used in the research context or in studies on the assessment of the impact of PC.
D	The principles for effective symptom control include a personalised evaluation and, if possible, the treatment of the aetiology or mechanism that underlines each symptom; an assessment of the pharmacological and non-pharmacological treatments available; the choice of the most simple, effective and convenient treatment guideline; information to the patient and his or her family on available options, and the consideration of their preferences.
D	The principles for effective symptom control include a personalised evaluation and, if possible, the treatment of the aetiology or mechanism that underlines each symptom; an assessment of the pharmacological and non-pharmacological treatments available; the choice of the most simple, effective and convenient treatment guideline; information to the patient and his or her family on available options, and the consideration of their preferences.

Pain treatment

D	When caring for pain in PC, an integral assessment of the pain should be made, bearing in mind its origin, aetiology, intensity and repercussion on the patient and family.
D	The team of professionals treating pain in PC should instruct and involve the patient and his/her family in the correct use of proposed analgesic measures.
C	When evaluating pain, validated scales can be used to quantify the pain. The use of visual analogue scales (VAS) or the Brief Pain Questionnaire (BPQ) is recommended.
D	The use of the WHO analgesic ladder together with adjuvant drugs, if necessary, is recommended in the pharmacological treatment of pain. The drugs must be used according to the intensity of the pain and the comorbility of each patient.
D	Criteria must be provided for administering analgesics. The response to the treatment must be monitored, adapting the dose individually.
A	Oral morphine is the treatment of choice on the third step of the analgesic ladder.
B	Tricyclic antidepressants are the drugs of choice in neuropathic pain. In the event of intolerance or contraindication, anticonvulsants (gabapentin) are recommended. Opioids can be used in neuropathic pain and they are the first option to be considered in the case of pain associated with another aetiology that requires a level of analgesia with these drugs. When response to the treatment is insufficient, drugs with different action mechanisms can be associated, monitoring the response and the adverse effects.

B	Morphine is the drug of choice in breakthrough pain (1/6 of the total daily dosage per dose). The alternative treatment is oral transmucosal fentanyl.
B	Alternative therapies do not constitute first line treatment for pain in patients in PC.
D	Patients with painful bone metastasis should receive analgesia according to the WHO ladder, starting with NSAID.
B	Radiation therapy is the treatment of choice in painful bone metastasis.
B	The use of bisphosphonates (pamidronate and zoledronic acid), depending on the type of tumour and its extension, is recommended in patients with painful bone metastasis with a prognosis of over six months.
B	Radioisotopes should not be used as first line of treatment for bone metastases, although they could be useful in selected cases, such as patients with prostate cancer when hormonal treatment has failed, or breast or lung cancer where radiation therapy, chemotherapy and bisphosphonates are contraindicated.

Asthenia, anorexia-cachexia

D	The initial assessment by the team of a patient with asthenia, anorexia-cachexia includes the identification, if possible, and treatment of the triggering causes; advice on daily activities, rest and sleep adapted to each situation, and an exploration of the expectations and beliefs about the diet of patients and carers.
A	Pharmacological treatment can be tested in selected cases where anorexia is a prevailing symptom, bearing in mind the accompanying symptoms, pharmacological interactions and possible side effects of the medication.
A	If pharmacological treatment is required, corticosteroids, in the first place, and megestrol acetate, as a second option, are the drugs of choice. The use of hydrazine is not recommended. Further studies with methylphenidate are required.

Dehydration

D	The oral route is the route of choice for liquid intake; the use of parenteral route must be avoided when possible.
D	The administration of liquids by parenteral route requires an individualised evaluation, weighing up advantages and disadvantages. This evaluation must include the patients' and their family's expectations on the administration of fluids.
B	If parenteral rehydration is chosen, the subcutaneous route can be considered in the first place, so long as the necessary means and prepared staff are available.
D	If the SC and endovenous routes are not possible the use of the rectal route can be considered.
√	If parenteral rehydration is chosen outside the hospital, hypodermoclysis is the first option that must be considered.

Breathing symptoms

Dyspnoea

D	The reversible causes of dyspnoea must be treated specifically, such as heart failure, exacerbations of COPD, cardiac arrhythmias, anaemia, pleural or pericardial haemorrhage, bronchial infection, pulmonary embolism or superior vena cava syndrome.
D	The intensity of the symptoms related by the patient should be evaluated.
B	If there is a lack of suitable evidence to be able to predict which patients can benefit the most from treatment with oxygen to alleviate the dyspnoea, it is advisable to evaluate the continuity of the treatment according to individual response.
A	Opioids by oral or parenteral route are first choice drugs for treating dyspnoea.
B	Promethazine can be used as a second line drug when opioids cannot be used or in addition to these. The use of benzodiazepines is not recommended for dyspnoea, except for situations of anxiety or panic, or in very advanced phases of life as an additional therapy to morphine (midazolam).
D	Corticosteroids are indicated in the case of dyspnoea produced by asthma, COPD, tumour obstruction of the airways or carcinomatous lymphangitis.

Coughing

D	Patients in PC with a cough require an individualised assessment to diagnose and, where possible, treat the specific causes of the cough. Palliative chemotherapy should be evaluated in cases of lung cancer.
D	To choose the drugs, it is recommended to evaluate other accompanying symptoms (pain, dyspnoea), the prior use of opioids, possible pharmacological interactions and administration route.
B	Dihydrocodeine, codeine, levodropropizine or cloperastine can be used as initial drugs.
C	Disodium cromoglicate can be used in patients with lung cancer whose cough does not respond to normal treatment.
D	If treatment is required for the cough, due to the COPD, codeine, dihydrocodeine or dextrometorphane can be used.

Superior vena cava obstruction

D	Patients with SVCO can be treated with corticosteroids, radiation therapy, and chemotherapy or stent implantation, depending on their general state, histological type of the tumour and its extension, as well as the availability of techniques.

Psychological and psychiatric symptoms

Delirium

D	The initial care of a patient with delirium should include the identification and treatment of the triggering causes, with special attention to the consumption of certain drugs (opioids); appropriate information to relations and carers and the evaluation of the need for pharmacological symptomatic treatment.
B	Haloperidol is the drug of choice to treat delirium.
D	Lorazepam can be added to haloperidol in the case of delirium with anxiety or unease.
D	Levomepromazine or, alternatively, midazolam can be used in delirium with non-controlled intense unease.
D	Hypodermoclysis can be used if delirium produced by opioids is suspected in dehydrated patients.
D	It is advisable to reserve the use of atypical antipsychotics for selected cases where haloperidol is contraindicated or is not tolerated. In situations such as dementias with Lewy bodies or in patients with Parkinson, where the use of haloperidol or risperidone is not recommended, other antipsychotics, such as olanzapine, clozapine or quetiapine can be resorted to.

Insomnia

D	A patient with insomnia should be appraised via a semi-structured interview aimed at assessing the factors related to insomnia: predisposing factors, sleep hygiene, symptom control, side-effects of medication and patient's expectations respect to sleep.
D	Attempt to correct the predisposing factors to insomnia or those trigger it, when possible.
D	An initial approach is recommended via a cognitive-behavioural strategy in all patients with insomnia.
D	The prescription of benzodiazepine or a benzodiazepine receiver agonist is recommended for patients who do not respond well to non-pharmacological treatment or who cannot wait for its application.
D	In cases of associated depression or lack of response to benzodiazepines, anti-depressants with sedative action can be used to treat insomnia.

Anxiety

D	The treatment of anxiety requires an individual assessment of the patient in EOL that includes the possible triggering causes, their adaptive state, and the stage of the disease, associated treatments and the patient's preferences.
D	The psychological support measures for the patient and family are the first thing that must be provided after the individual assessment.

D	Pharmacological treatments are recommended when the psychological support is not sufficient. BZD can be used, preferably those with short or intermediate action.
√	In the case of anxiety associated with depression, delirium, dyspnoea or intense pain, tricyclic antidepressants, haloperidol or opioids, respectively can be used.

Depression

D	The initial assessment of depressed patients in PC includes: identifying and addressing potentially treatable causes, evaluation of adverse effects and interactions of previous pharmacological treatments and estimation of the possible risk of suicide.
B	The initial therapy of depressed patients in PC includes psychosocial structured interventions, including psychotherapy by the personnel of the care team, and, if necessary, by specialised personnel within a structured programme.
B	If necessary, antidepressant drugs can be used (SSRI or tricyclic), bearing in mind their pharmacological properties, other drugs the patient receives and his or her symptom profile at each given time.
D	Psychostimulants, such as methylphenidate, can be used as an alternative to tricyclic antidepressants and SSRI, above all when a rapid start of the antidepressant effect is required or in cases with very short life expectancy.

Digestive symptoms

Mucositis

D	Preventive pharmacological treatment must be indicated in agreement with the risk of developing mucositis. This risk is based on the clinical situation and on the modality and dosage of the treatment (radiation therapy or chemotherapy).
B	Prevention via drugs or local measures (hydrolytic enzymes, ice tablets, benzydamine, zinc sulphate) or parenteral (amifostine) can be carried out in selected cases.
B	There is not sufficient evidence to recommend the treatment of mucositis with mouthwashes of allopurinol, granulocyte growth stimulating factors or immunoglobulins, so the basis of the treatment is careful hygiene of the mouth and analgesics.
A	Analgesics controlled by the patient can be used to reduce the dose of morphine in the treatment of pain caused by mucositis.

Dry mouth (xerostomia)

D	In patients with xerostomia, salivation stimulants, ice or artificial saliva can be used as well as mouth hygiene.
A	Pilocarpine is indicated if pharmacological treatment of the xerostomia is required, bearing in mind its benefit and the possibility of side-effects.

Candidiasis

B	Candidiasis not directly related with radiation therapy or chemotherapy can be treated firstly with external use antifungal agents (preferably miconazole or clotrimazole) and, if necessary, oral antifungal agents (itraconazole and fluoconazole).
A	Treatment with ketoconazole, fluconazole and clotrimazole (50 mg) can be used in cancer patients with oral candidiasis after immunosuppression treatment.
A	Antifungal agents that are totally or partially absorbed in the gastrointestinal tract (fluconazole, ketoconazole, itraconazole, miconazole and clotrimazole) are the drugs of choice to prevent oral candidiasis in cancer patients with neutropenia or a high risk of suffering from it, who are going to receive treatments with chemotherapy and radiation therapy.

Dysphagia

D	The treatment of dysphagia requires a personalised evaluation to identify and, if possible, treat the different causes involved.
D	The diet must be adapted to the clinical characteristics of the dysphagia. A soft diet is recommended, in agreement with each patient's tastes. In the case of dysphagia due to liquids, thickeners can be used.
D	A short cycle of corticosteroids can be tried in the case of obstructive dysphagia due to tumour invasion.
D	The team, the patient and his or her carers can decide on the use of a nasogastric probe or the execution of ostomies on the case of serious dysphagia that does not respond to the treatment and that prevents oral feeding.

Nausea and vomiting

√	Treatment of nausea and vomiting in EOL patients requires a meticulous evaluation of the aetiology and the factors involved (endocranial hypertension due to tumour invasion, metabolic disorders, drugs, visceral affection, etc.) to be able to carry out personalised treatment.
D	The prophylaxis of nauseas and vomiting should be based on the risk of emesis in patients who receive chemotherapy or radiation therapy.
B	The association of 5HT3 antagonists (such as ondansetron) and corticosteroids is recommended in vomiting induced by chemotherapy with a moderate or low risk of emesis.
B	The association of 5HT3 antagonists, corticosteroids and aprepitant is recommended in vomiting induced by chemotherapy with a high risk of emesis.
D	Corticosteroids, domperidone, metoclopramide or combinations of corticosteroids with metoclopramide or domperidone can be used, depending on the intensity of the symptoms, in irruptive vomiting after treatment with chemotherapy or radiation therapy.
B	Metoclopramide is the treatment of choice in patients with nauseas and vomiting with no relationship with chemotherapy or radiation therapy. 5HT3 antagonists can be added to traditional therapy in the case of a limited control of symptoms.

B	Psychotherapy using behavioural techniques can be used in anticipatory vomiting. Alprazolam and lorazepam can be used as additional therapy to the counselling and to the psychotherapy.

Constipation

√	The presence of faecalomas must be ruled out before prescribing treatment with laxatives.
A	The use of laxatives is recommended (sen, lactulose alone or associated with sen, polyethylenglycol, magnesium salts and liquid paraffin) together with an adequate diet (sufficient hydration and fibre) and adapted exercise.
B	The prescription of opioids must be accompanied by constipation preventive measures, including laxatives.
D	Laxatives by rectal route (suppositories or enemas) can be used in the case of faecal impaction.

Diarrhoea

D	The treatment of diarrhoea in PC requires the identification of possible correctable causes, the evaluation of the degree depending on the rate of bowel movements and the affection of the general state, and an initial treatment with diet and intake of appropriate liquids.
B	Loperamide is indicated when diarrhoea of non-infectious origin persists, including stages 1 and 2 produced by chemotherapy or radiation therapy.
D	Loperamide is indicated in cases until 12 hours elapse without bowel movement. In the case of radiation therapy, it is indicated for the time the treatment lasts.
B	Subcutaneous octreotide can be used (including the use of infusion pumps) in selected cases in the case of refractory diarrhoea.

Bowel obstruction

D	Patients with LBO require an individual evaluation that bears in mind their functional situations, including surgical contraindications; the location of the obstructions; their preferences, the availability of surgical or endoscopic techniques or experience with them in the setting where the patient is treated.
C	Surgery and the endoscopic placement of self-expanding metal stents (SEMS) can be used in selected patients with LBO.
C	The medical treatment of bowel obstruction must include analgesics, antiemetics and antisecretory drugs. Corticosteroids and butylscopolamine can be used as additional therapy.
√	If there is a lack of response to the previous measures octreotide can be used.

Ascites

D	Paracentesis can be used in the case of malignant ascites that requires symptomatic treatment.
D	Treatment with diuretics can be considered in very selected cases where the presence of high levels of renin is suspected, and in ascites due to advanced cirrhosis.
D	Peritoneovenous shunts can be considered in selected cases following the failure of the previous measures.

Hiccups

D	Treatment of patients with persistent or untreatable hiccups requires a meticulous evaluation and the treatment of possible causes. If the hiccups persist, treatment with physical measures must be attempted.
D	Pharmacological treatment (baclofen, metoclopramide, haloperidol, nifedipine or gabapentin) can be used if necessary, bearing in mind the interactions and side effects in each case. Bacofene is the initial drug if there is no contraindication for its use. It can be used alone or combined with omeprazole.
D	In the case of untreatable hiccups, and following the failure of oral therapy, parenteral midazolam can be used.

Skin Care

Prevention and Treatment of Ulcers

D	The prevention measures of pressure ulcers(PUs)include: changes in posture, adequate nutrition, not raising the head of the bed more than 30 degrees and maintaining adequate cleanliness and hydration.
A	Special support surfaces are recommended in patients with a high risk of developing PU.
A	The use of hyperoxygenated fatty acids is recommended in patients with a high risk of developing PU.
D	The type of dressing should be chosen depending on the stage and characteristics of the ulcer, on the objectives and patient's preference.
D	Metronidazole administered externally can be used to reduce the smell in fungating wounds.
B	6% miltefosine solution can be used externally to curb the evolution of fungating wounds.

Pruritus

D	Initially managing a person with pruritus consists in identifying and, if possible, specifically treating the underlying causes, with special emphasis on the drugs. Aggravating factors, such as alcohol, spicy food, heat, the use of tight clothing, the use of soap with detergents, etc. must be avoided.

D	General skin care must be provided, including sufficient moisturizing and prevention of injuries caused by scratching.
D	Pharmacological treatments will be administered if necessary depending on the origin of the pruritus (opioids, uremic, cholestatic, paraneoplastic, dry skin). Treatment may change depending on the therapeutic response, following the outline proposed in table 26.

Urinary Symptoms

Urinary urgency

D	Due to the lack of evidence about what is the best treatment for urinary urgency in PC, anticholinergic, antispasmodic drugs, NSAID, corticosteroids and local anaesthetics can be used.

Emergencies

Hypercalcaemia

√	The possibility of hypercalcaemia must be considered in patients in PC with a worsening of their general state without a clear cause that explains it.
A	The treatment of choice for serious hypercalcaemia is hydration together with hypocalcaemiant drugs.
A	IV bisphosphonates are the drugs of choice for acute hypercalcaemia; high doses of powerful amino-bisphosphonates (such as zoledronic or pamidronic acid).
D	SC or IM salmon calcitonin can be used during the first hours, continuing later with bisphosphonates.
D	Corticosteroids can be used in haematological tumours or in patients with hypervitaminosis D due to granulomatosis.

Spinal Cord Compression

D	If SCC is suspected, an NMR must be requested to confirm the diagnosis.
√	The suspicion of SCC requires the patient to urgently be referred to perform an appropriate study and treatment.
D	An individual evaluation must be carried out on patients with SCC, including level and number of spinal compressions, type of tumour and extension, vital and functional prognosis, degree of neurological affection, patient's preferences and availability of treatment with radiation therapy and surgery.
C	The treatment must be carried out as soon as possible.
B	High doses of corticosteroids are recommended, both in treatments with radiation therapy and with surgery.

D	Radiation therapy as the only treatment is preferable in the case of contraindication of surgery, radiosensitive tumours, established paraplegia, compression at several levels, surgery failure or patient's wishes.
B	Surgery combined with radiation therapy is the treatment of choice in selected patients with a vital prognosis of more than 3 months.

Seizures

D	The initial management of a patient with seizures in PC must include the identification and treatment of the possible triggering causes and instructions to the patient's carers, including the possibility of administering anticonvulsant medication.
D	Epileptic status is a medical urgency that requires urgent referral to hospital.
D	The initial treatment of seizures is IV or rectal diazepam. The alternative option is subcutaneous midazolam.
D	If treatment is required to prevent new crises, the treatment must be chosen at an individual level, bearing in mind the types of crisis; the experience of use; the side effects and the possibility of pharmacological interactions, including chemotherapy.

Bledding

D	The patient's carers must be warned and prepared for the risk of the possibility of massive bleeding.
D	The availability of urgent care must be offered with the longest time coverage possible, including a direct telephone contact for the case of massive bleeding.
D	The preparation of a plan of action is recommended for risk patients, with instructions for carers, including the following: a) Place a bowl and dark-coloured towels at the patient's head to compress the point of haemorrhage and absorb and dissimulate the blood. b) Place the patient on his or her side in case of haematemesis or haemoptysis to prevent choking. c) Prepare a syringe preloaded with midazolam to carry out emergency sedation with 5-10 mg administered parenterally, preferably subcutaneously – the process will be made easier if a syringe driver has been previously inserted-, which could be repeated if necessary.

Psychosocial and spiritual support to the person in EOL

B	The psychosocial well-being of patients with life-threatening diseases must be evaluated on a regular basis.
D	The psychosocial assessment of the patient in PC should include the following fields: aspects related to the moment in life, meaning and impact of the disease, coping style, impact on the perception of self, relations (type of family, friends, etc.), sources of stress (economic difficulties, family problems, etc.), spiritual resources, economic circumstances, doctor-patient relationship, social resources network (socio-health centres, social workers, etc.).

B	Health professionals who care for patients in PC should offer them basic emotional support.
D	Patients with significant levels of psychological suffering should be referred to receive specialised psychological support.
D	The training of health professionals in psychosocial support techniques should be promoted.
C	Increasing awareness and establishing common objectives are the first step to build bridges between health and social workers of hospital and community fields.
D	The team caring for a person in PC should bear in mind his or her spiritual beliefs and needs.
D	Failing appropriate evidence on how to best provide spiritual support, it is recommended to offer this support as an integral part of the care, whatever the health-care context, and with the approach based on effective communication principles.
D	It is important to consider the cultural differences with respect to spirituality. This must not justify a lack of attention to these aspects in people who belong to different cultural groups to our own.

Psychosocial support to the family

C	Carers must be offered the possibility of expressing their needs for support and information.
D	It is recommended to offer basic emotional support to carers.
C	The service planning for the carers should include the following premises: a) The services must be focused on the carers' needs. b) The accessibility and acceptability must be evaluated at the onset. c) The objectives must be clear and modest. d) The results should be assessed.
D	It is advisable to offer the most vulnerable or depressed carers intensive psychosocial support or specialised services.

Care during the last days. Agony

D	The appropriate care during the last days of life should include: a) Informing the family and carers about the close death situation and, in general, the necessary and appropriate information according to needs. b) Explaining and reaching a consensus about the care plan with the patient and his or her family. c) Evaluating the medication taken by the patient, suspending non-essential drugs after explaining the reasons. d) Treating the symptoms that produce suffering. The necessary drugs must be available if the patient is at home. e) Interrupting interventions or unnecessary or futile tests, according to the patient's desires.

	f) Evaluating the psychological, religious and spiritual needs of the patient, his or her family and carers. g) Providing care in a calm environment, respecting intimacy and facilitating the proximity of family and friends. h) Providing the ways and necessary resources for hospitalisation and for home-care.
D	Premortem death-rattles should be treated via the use of SC scopolamine butyl bromide.

Palliative sedation

D	The palliative sedation process or in agony requires: a) A correct therapeutic indication carried out by the doctor (existence of a refractory psychic or physical suffering or symptom at the end of the patient's life), and if possible, validated by another doctor. b) Professionals with clear and complete information about the process, recorded in the medical history. c) Administration of drugs in the necessary dosage and combinations to reach an adequate sedation level. d) The explicit consent of the patient or family if the patient is incompetent.
D	The correct prescription of palliative sedation in agony requires: a) Careful assessment of the end of life diagnosis. b) Presence of refractory psychic or physical suffering or symptoms. c) Assessment of the patient's competence when making decisions.
D LG	Verbal consent is considered sufficient, although it may at times be given in writing. Record must always be kept in the medical history. In non-competent patients, the consent must be given in the following order: a) First, by consulting the Registry Living Wills or Preliminary Instructions. b) In the absence of preliminary instructions, the medical team must evaluate the patient's desires with the family or close friends, considering the previously expressed desires and values. c) In the absence of b), sedation should be agreed with the family.
D	The use of midazolam is recommended as first option for sedation for the majority of the symptoms, and levopromazine when delirium is the prevailing symptom.
D	The patient's level of sedation should be monitored, using the Ramsay scale for this.

Bereavement

D	The risk of complicated bereavement should be identified based on the following: a) Risk factors. b) Clinical judgement. c) Information about the family environment (genogram) or originating from this. Studies are required to appropriately evaluate the validity of the available scales (such as the Parkes & Weiss Risk Index).

B	Formal or organised interventions are not recommended in normal bereavement.
D	In normal bereavement it is recommended to provide information about bereavement and about the available resources, and basic emotional support.
B	In risk bereavement it is recommended to carry out regular monitoring, with emotional support, individually evaluating the need for specific and structured psychotherapies.
B	It is recommended to refer the person with complicated bereavement to specialised services (psychology, psychiatry, etc.) to receive specific and structured care.
D	Professionals caring for patients in EOL and their relations should have access to elementary training in bereavement to qualify them to provide basic care to the bereaved, understand and explore their needs, evaluate risk factors, and detect people with complicated bereavement and refer them to a specialised service.

1. Introduction

Population ageing and the increasing number of people with chronic-degenerative diseases and with cancer represent an important challenge for health services in developed societies. At the end of their lives, many of these patients undergo intense suffering and require health and social care that involves all the health-care fields.

It is estimated that in Spain 50 to 60% of the people who pass away have gone through a process of impairment during the last year of their lives (1). It is estimated that between 8 and 22% (2-4) of hospitalisations may correspond to patients in this period.

There is also a generalised demand, in our society, for quality care with a focus on people and at reasonable costs, which will permit a decent life and death. This reality reveals the need to reconsider the objectives that present-day medicine must pursue, as this, until now, has focused too much on a curative approach. Callahan, in an article published in the year 2000 (5), defended the recognition of death in peace as an objective of the same value and importance as the fight against diseases and the prolongation of life.

The objectives of palliative care (CP) include alleviating suffering and improving, whenever possible, the quality of life and dying process of people. PC has progressed considerably in our country over the last few years. However, as included in the Palliative Care Strategy of the National Health System, there are still areas for improvement (1):

- The need to reorientate the eminently curative objectives of present-day medicine towards others that avoid considering death as a failure of medicine.
- The promotion of training in palliative medicine.
- The reduction of variability among the different autonomous communities, both in the organisation of care and in the procurement of care, with the aim of avoiding inequalities within the National Health System.
- The need for an integral approach of the care it covers, as well as symptom control, emotional, social and spiritual aspects of the patients and of their carers or relations, as well as care in bereavement.
- The need to improve the accessibility to PC for all patients that need it.
- The promotion of multidisciplinary work and the coordination between the different health-care levels, services and professionals involved.
- The importance of information and communication with the patient and his or her family as one of the basic points, together with the need to foster the autonomy and participation of the patient and of his or her family in decision-making.
- The need for the team to come closer to responding to the needs of the patients and their families.
- The promotion of programmes dedicated to non-cancer patients.

PC is considered as a priority health intervention area in all the autonomous communities, according to the situation survey carried out by the Ministry of Health and Consumer Affairs in 2006 (1). Amendments to the recent legislation also show the importance of PC in Spain. The Law on Cohesion and Quality of the National Health System states that PC is a service that must be present at any health care level (6). Royal Decree 1030/2006 (15.09.2006), which establishes the

portfolio of common services of the National Health System, includes the minimum demandable content in PC, both for primary health care services and for specialised care services. This content covers the identification, integral and frequent evaluation of symptoms, information and referral of patients to specialised areas in case of complexity.

There are several national approaches to the execution of CPGs in PC in our setting. Scientific societies such as the Spanish Society for Palliative Care (http:// www.secpal.com/guiasm/index.php) and some health services (such as Extremadura and Andalusia) have prepared guidelines on the topic. Some of these documents deal with partial aspects of PC, such as sedation or bereavement (7; 8). The majority are based on reviews of literature, although there are only a few that grade the recommendations (9).

The National Strategy establishes a series of priorities that include the «need to prepare clinical practice guidelines and protocols agreed by consensus and based on scientific evidence» (1).

2. Scope and objectives

The objective of this CPG is to act as an instrument to improve the health care of people in the end-of-life phase (EOL) and of their families, in the different settings and centres where care is provided (hospital, primary health care, home, specialised services, emergency services, centres for social health, etc.

The GPC sums up the available evidence for key questions of PC and aims to make decision-making easier for clinicians. It does not seek to substitute clinical judgement.

It approaches the following aspects of PC, both in cancer and non-cancer patients: communication with the patient and his or her family, symptom control, psychosocial and spiritual support, family care, care in agony, sedation and bereavement. An exhaustive approach of all the areas of PC has not been sought, and the scope of the CPG has been limited to the adult population. Some aspects have been excluded, such as nutrition or very specific treatment techniques (such as invasive therapies for pain, the different specific types of psychotherapy, etc.) or emotional aspects that affect the members of the teams that provide PC.

Although the assessment of the evidence includes points relating to the organisation of PC, the planning of the health services of the different autonomous communities is not a mission of this guideline. Due to the great differences that exist between communities and health services regarding the organisation and procurement of PC and the fact that these are under development in our country, no indicators have been included to implement the CPG. This aspect can be approached in future reviews of the guideline.

The main users of this guideline are primary and specialised health care professionals; hospital medical and surgical specialists of the different services, medical, psychological and nurse practitioners of palliative care units and home hospitalisation units; emergency service, intensive care and social-health centres professionals, carers and patients.

3. Methodology

Methodology. Levels of evidence and formulation of recommendations

The methodology used is included in the CPG Preparation Manual in the National Health System[1].

The steps given below have been followed:

- Constitution of the guideline preparation group, integrated by professionals: from primary health care (medicine, nursing, pharmacy), specialists in palliative care attached to hospital units, in oncology, internal medicine, home hospitalisation and specialists in methodology. A focal group has been carried out to incorporate the vision of the carers.
- Formulation of clinical questions following the Patient / Intervention / Comparison / Outcome or Result format.
- Bibliographic search in: Cochrane Library, PsycINFO, DARE, Medline Pubmed, Evidence Based Review, Embase, CINHAL, Joanna Briggs Institute, IME, manual search in the Palliative Medicine magazine, search for qualitative studies in Spanish.

  Due to the lack of randomised or observational studies in many PC areas, the following have been consulted, *Oxford Textbook of Palliative Medicine*[2], the *Oxford Handbook of Palliative Care*[3], the guideline of the la SEC PAL[4], a monographic number on CP in the magazine *Primary health care* and several clinical practice guidelines (9; 10; 11; 12). Furthermore, an additional search has been carried out on the website http://www.care-search.com.au/home/Default.aspx.

  Inclusion of studies published in English, French and Spanish.
- Assessment of the quality of the studies and summary of the evidence for each question, following the recommendations of SIGN-50 (Scottish Intercollegiate Guidelines Network)[5].
- Formulation of recommendations, based on the «formal assessment» or «reasoned judgement» of SIGN. Classification of the evidence and grading of the recommendations has been carried out in agreement with the SIGN criteria (appendix 1). Controversial recommendations or cases where evidence is lacking have been solved by consensus within the preparation group.

[1] Working Group on CPG. Preparation of Clinical Practice Guidelines in the National Health System. Methodology Manual [Internet]. Madrid: National Plan for the NHS of the MSC. Aragonese Institute for Health Sciences I+CS; 2007 [10/1/08]. CLINICAL PRACTICE GUIDELINES IN THE NHS: I+CS No. 2006/0I. Available athttp://www.guiasalud. es/.

[2] Doyle D, Hanks G, Chreney N, Calman K. Oxford Textbook of Palliative Medicine. Third ed. Oxford: Oxford University Press; 2004.

[3] Watson MS, Lucas C.F, Hoy AM, Back IN. Oxford Handbook of Palliative Care. New York: Oxford University press; 2005.

[4] Sanz Ortiz J, Gomez-Batiste X, Gómez Sancho M, Nuñez-Olarte JM. Palliative Care Handbook. Recommendations of the Spanish Society of Palliative Care (SECPAL). Madrid: Guidelines and Handbooks of the Ministry of Health and Consumer Affairs. Ministry of Health and Consumer Affairs. Technical General Secretariat; 1993.

[5] SIGN. A guideline developers' handbook. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2001.

The assessment of evidence and formulation of recommendations in the field of PC are especially problematic. The evidence classification systems and grading of recommendations used until now do not adapt well to the type of evidence that is assessed in the field of PC. There are considerable initiatives that have carried out reviews or research into PC but the majority of them originate from very different health care contexts to ours.

The systems to develop CPG guidelines place a lot of importance on randomised clinical trials (RCT) or the systematic review of RCTs, which provide the highest level of evidence. In many questions on PC the execution of RCTs presents methodological and ethical difficulties. There are many areas that lack RCTs, even for treating normal symptoms (2). The absence of evidence on PC in non-cancer patients is striking.

On the other hand, aspects such as quality of life, communication, comfort or welibeing of the patient and of his or her carers are variables whose results are difficult to evaluate through traditional RCTs. However, they are probably the most important for patient and carers (2). The evidence obtained from qualitative research is very relevant in this field but the methodology on its integration with the results of the quantitative studies to formulate recommendations in the CPG is currently undergoing discussion and development. We have chosen to indicate the qualitative studies as «Q» in this guideline.

Another peculiarity in this field is the existence of numerous systematic reviews that include different types of designs (RCT, observational, descriptive, qualitative studies, etc.).

Throughout this CPG, its users will find many recommendations based on consensus, qualified with the letter «D» or the symbol «√» (see appendix 1). This fact reflects two circumstances mentioned above: insufficient research and lack of adaptability of the recommendation formulation systems.

The tables including evidence levels and grades of recommendations can be referred to in appendix 1.

On the other hand, the people this CPG is aimed at need to know the legal regulation that exists in our country on different aspects related to PC. Those questions where the recommendations derived from the legal regulation are especially important have been identified with the letters «LG».

- Expert collaboration for the formulation of questions and review of the first draft guidelines. Physicians (primary health care, oncology, psychiatry, home hospitalisation, intensive care, palliative care units, geriatrics, internal medicine), psychologists and home hospitalisation unit nurses have taken part in this group.
- The review has been carried out on the second draft.
- The different Scientific Societies involved have been contacted (Spanish Society of Palliative Care (SECPAL), Spanish Society of Primary Health Care Pharmacists (SEFAP), Spanish Society of Geriatrics and Gerontology (SEGG), Spanish Society of Home Hospitalisation, Spanish Society of Family and Community Medicine (SEMFYC), Spanish Society of Intensive Care, Critical Medicine and Coronary Units (SEMICYUC), Spanish Society of Internal Medicine (SEMI) and Spanish Society of Medical Oncology (SEOM)), which are also represented through the preparation group and expert collaboration.
- This document forms the «complete» CPG on Palliative Care. The CPG is organised into chapters that give answers to the questions that appear at the beginning. A summary of the evidence and recommendations are presented at the end of each chapter. The type of study and the possibility of bias of reviewed bibliographic sources is given in the right-hand

margin, throughout the entire text. There is an «abridged» shorter version of the CPG, with the main appendices of the «complete» CPG.

- This CPG is available on the portal of GuiaSalud (http://www.guiasalud.es/).
- The update of the CPG is foreseen for every five years, though a more frequent update of its online version has not been ruled out.

4. Introduction to palliative care

4.1. Definition and objectives of palliative care

The World Health Organisation (WHO) (13) defines *palliative care* (PC) as «the approach that improves the quality of life of patients and their families facing the problem 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». It considers that the social-health team must approach the patients and their families with the aim of responding to their needs, and it lists the following characteristics of palliative care:

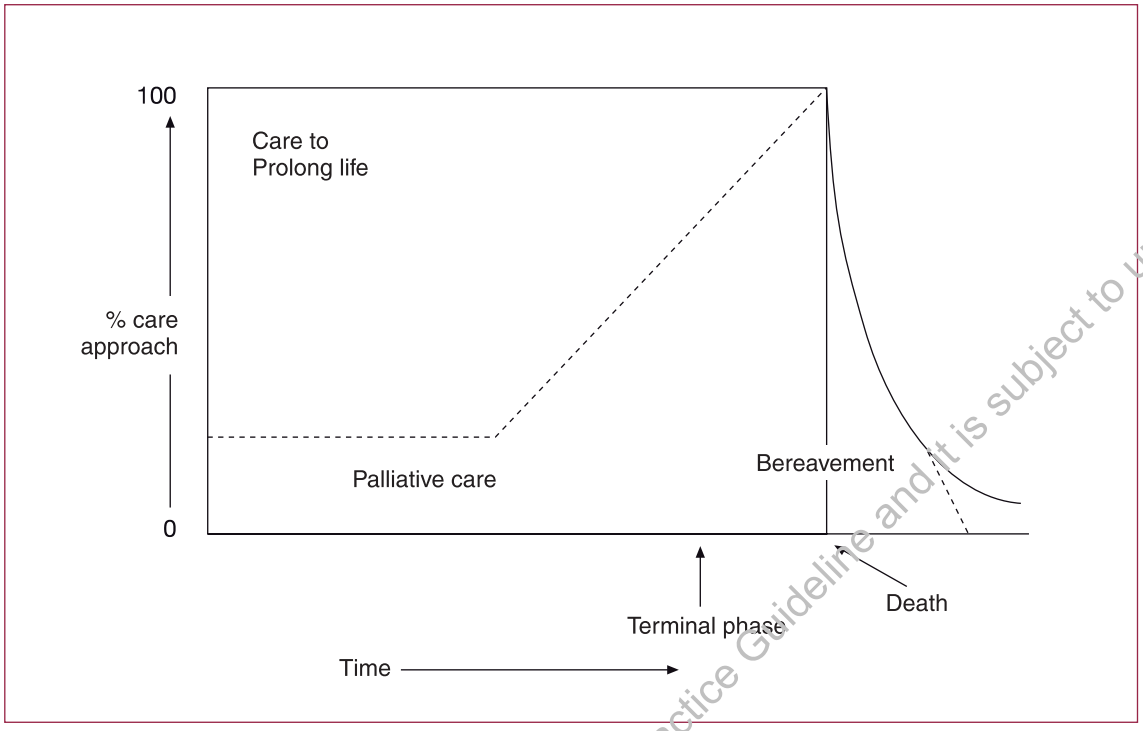
- Provides relief from pain and other distressing symptoms.
- Affirms life and regards dying as a normal process.
- Intends neither to hasten or postpone death.
- Integrates the psychological and spiritual aspects of patient care.
- Offers a support system to help patients live as actively as possible until death.
- Offers a support system to help the family COPE during the patient's illness and in their own bereavement.
- Enhances the patient's quality of life.
- 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, etc.).
- Also includes investigations needed to better understand and manage distressing clinical complications.

This concept of PC recognises that people with illnesses other than cancer, which are irreversible, progressive and have a terminal phase, can also benefit from its application. These can, for example, be patients with chronic obstructive pulmonary disease (COPD), dementia, heart failure, advanced renal or hepatic failure or neurological illnesses (such as strokes, Parkinson's, multiple sclerosis or amyotrophic lateral sclerosis, among others) (1; 10; 11).

As shown in figure 1 (11), PC should commence in the early phases of the diagnosis of a life-threatening illness, at the same time as the curative treatment. Likewise, even in the final phases of the illness, where treatment is mainly palliative, there may be a space for attempts aimed at curative measures. On the other hand, bereavement may require care throughout a prolonged phase.

Thus, the transition from curative care to palliative care is often gradual and must be based on the individual needs of the person rather than on a specific expected survival time (1; 10).

Figure 1. Adapted from the University of California with permission from Steven Z. Pantilat, MD, FACP



The promotion of wellbeing and the improvement of the quality of life are among the general objectives of PC, and the following is considered necessary (1):

- Appropriate information and communication to assure the patient and his or her family that they are being listened to and that they will obtain clear and sincere answers. Furthermore, they will be given the emotional support they need, so that they can express their emotions and participate in the decision-making with respect to their lives and to the dying process in agreement with the applicable laws.
- Care of pain and other physical symptoms, as well as emotional, social and spiritual needs, not forgetting the practical aspects of the care of patients and their families.
- Health-care continuity guaranteed throughout its evolution, establishing coordination mechanisms between all the health-care fields and services involved.

4.2. Relevant concepts

4.2.1. Quality of life

Quality of life is a multi-dimensional, dynamic and subjective concept for which there is no reference pattern and which is consequently difficult to define and measure (14). In the context of PC, *quality of life* focuses on different aspects of patients such as their physical or mental capacity, their ability to lead a normal life and a satisfactory social life, the achievement of personal goals, feelings of happiness and satisfaction, as well as the existential or spiritual dimension. Thus, four

fields can be identified in quality of life: physical, psychological, social and spiritual wellbeing (14).

Gill & Feinstein, after carrying out a review of the literature in 1994 about the instruments for measuring the quality of life (15), concluded that the approach of these instruments was not the most suitable. They set forth some recommendations: use global evaluations of the patient (one on the global quality of life and another on the health-related quality of life), measure the gravity and importance of different problems, and include open-ended questions when using any of the available instruments.

The patient is the person that can most appropriately evaluate his or her quality of life. When the patient is not capable of providing the required information, the family and close friends or health professionals can supply useful information, especially on specific and objective aspects (14).

There are instruments now that have been validated in the Spanish language to measure the quality of life in cancer patients in PC, such as Rotterdam Symptom Checklist (16), Palliative Care Outcome Scale (POS) (17) or the EORTC QLQ-C15-PAL scale (18) (appendix 2).

4.2.2. Suffering

Encountering a terminal illness is a cause of great distress to patients, their families and their professional carers. Formulating a therapeutic answer requires understanding the phenomenon of suffering and of the factors that contribute to it. It is not strange that health professionals link physical symptoms to suffering and, although the presence of these symptoms is usually an important precedent, they are not the only source of suffering. Failure to assess suffering may cause confusions in the therapeutic strategies (19).

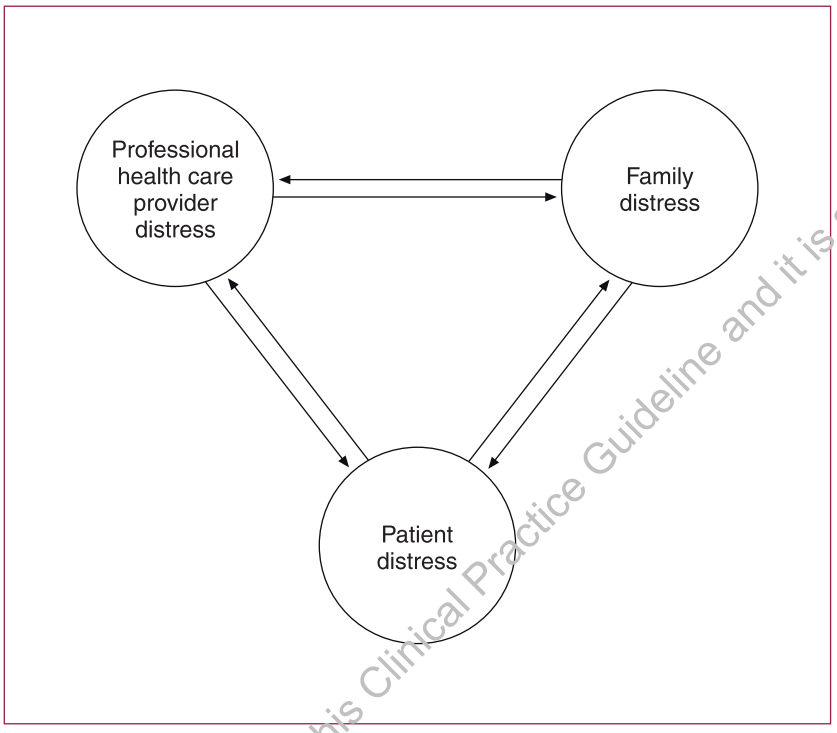
Suffering has been defined by Chapman & Gavrin (20) as «a complex negative cognitive and affective state, characterised by the perceived threat to the integrity of self, associated with a negative affective quality and inability to cope because of exhaustion of personal and psychosocial resources».

The interrelated elements of suffering in terminal illness (patients, family and health carers) (19) have been conceptualised through the triangular model of suffering (figure 2). According to this model, the suffering of each one of these three groups may amplify the distress of others. Sources of suffering are:

- In the patient: physical symptoms (such as pain), psychological symptoms and existential suffering (hopelessness, meaninglessness, deception, remorse, anxiety faced with death and alteration of the personal identity), suffering of family and friends, as well as the perception of being a burden for self and for others.
- In family, friends and carers: psychosocial factors, emotional tension, uncertainty, feeling of impotence, fear of the patient's death, alteration of roles and lifestyles, economic problems, perception that the services are inadequate, sadness and sorrow of the patient's impairment (anticipation of loss), burden of the carers (physical work, emotional work, tiredness), the economic effort that must be made due to the costs generated by caring for the patient, and the conflicts that may be created in the carers (between the desire to provide adequate care and at the same time the desire to accelerate death).
- In health professionals: constant exposure to suffering and to loss, frustration, impotence and the feeling of failure, excessive occupational pressure with the perception of lack of

resources (material, human, time), the difficulty to take therapeutic decisions, difficulties in communication and in the relationship with the patient and family members, the high expectations of the latter, etc. All of these are factors that can contribute to exhaustion and to *burnout*.

Figure 2. Triangular Model of Suffering



Ramón Bayés (21) proposes an instrument to detect the stages of distress, regardless of the cause or causes that produce it: the subjective perception of time. It is comprised of two questions:

— How did time pass yesterday – tonight, this morning, this afternoon- short, long.. what would you say?

— Why?

The first of them constitutes an indicator of distress-wellbeing, whilst the second provides information about the cause or causes of the possible distress. These questions help go deeper into how this distress is perceived by the patient as an important threat to his or her physical or psychological integrity. They also make it possible for patients to vent their emotions and contribute to the knowledge or cause giving rise to the distress. They also indicate the type of medical, social, psychological or spiritual intervention necessary to try to alleviate it (22).

To conclude, distress or suffering is a complex human experience that requires multi-dimensional assessment to construct an efficient therapeutic alternative so as to adequately answer the patient's and the family's problems. Health professionals must carefully assess each case, identifying the patient's needs and formulating a multi-disciplinary intervention aimed at solving or palliating these needs. Continuous assessment or monitoring must also be carried out in order to modify the care plan as new problems arise or the needs of the sick person and of his or her family change.

4.2.3. Autonomy

Quality of life, distress and the balance between the benefits and disadvantages of interventions provoke value judgements whose meanings may differ a good deal from one person to another. So, when communicating with the patient and his or her family to inform them or propose different therapeutic alternatives, it is essential to know their desires.

The patient's autonomy is one of the four basic principles of bioethics, the basis of medical deontology and key in the context of good health practice, which takes on special importance in the end of life decisions. Autonomy is understood as the ability to carry out acts with full awareness of the consequences, sufficient information and without internal or external coercion (1).

The patients' right to autonomy is included in basic Law 41/2002 (14.11.2002) regulating the patient's autonomy and on the rights and obligations in clinical documentation and information matters. This law recognises that the sick person is entitled to freely decide, after receiving the adequate information, between the available clinical options. It also recognises that any patient or user is entitled to refuse the treatment, except in the cases determined by law.

Furthermore, a specific legislation has appeared in almost all the autonomous communities[6], in a short period of time, whose aim is to develop and specify how a citizen can make decisions about the medical actions he or she wants or does not want to receive in situations where, due to his or her incapacity, he or she cannot communicate with the health professionals. In other words, it is a clear living will, explicitly declared, that is directly binding for professionals responsible for making health decisions (23).

4.3. Organisational aspects of palliative care

The formulation of evidence-based recommendations on PC models for our setting is not the objective of the CPG. However, it is important to carry out a bibliographic review on some key aspects of the organisation of PC, bearing in mind the organisational heterogeneity in our country. It is deduced from the assessment of the qualitative study carried out for this CPG that the way to organise the PCs and the coordination between the different professionals that provide them has a considerable impact on the patients and their families.

Qualitative study Q

The patient is entitled to receive PC in different fields and services, at home, hospital or at centres for social health. These services must work in a coordinated manner to guarantee that the needs of both patients and carers are attended without any loss in continuity (12).

Expert opinion 4

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2 **Catalonia:** Catalan Law 21/2000 (29.12.2000). **Madrid:** Law 12/2001 (21.12.2001), of the Parliament of Madrid. **Aragon:** Law 6/2002 (15.04.2002), of the Parliament of Aragon. Decree 100/2003 (6.05.2003), of the Government of Aragon. **La Rioja:** Law 2/2002 (17.04.2002), of the Parliament of La Rioja. **Navarra:** Foral Law 11/2002 (6.05.2002) of Navarre. **Community of Valencia:** Law 1/2003 (28.01.2003), on rights and information to the patient of the Community of Valencia. **Castile-Leon:** Law of Castile-Leon 8/2003 (8.04.2003), on rights and obligations of people related to health. **Andalusia:** Law 5/2003 (9.10.2003), on statement of living will, of the Parliament of Andalusia. **Basque Country:** Law 7/2002 (12.12.2002), on living wills in the field of health, of the Basque Parliament. Decree 270/2003 (4.11.2003), whereby the Basque Registry of Living Wills is created and regulated. **Galicia:** Law 3/2001 (28.05.2001),; Law 3/2005 (7.03.2005). **Extremadura:** Law 10/2001 (28.06.2001). Law 3/2005 (8.07..2005). **Cantabria:** Law 7/2002 (10.12.2002). **Balearics:** Law 5/2003 (4.04.2003). **Castile La Mancha:** Law 6/2005 (7.07.2005). Decree 15/2006 (21.02.2006). **Murcia:** Decree 80/2005 (8.07.2005). **Canary Islands:** Decree 13/2006 (8.02.2006). **Asturias:** awaiting creation. **National Registry of preliminary instructions:** Royal Decree 124/2007 (2.02.2007), whereby the national Registry of preliminary instructions is regulated as well as the relative computerised personal data file.

The organisational type objectives consist in guaranteeing that the services are available for all patients that need them and when they need them; they should be quality objectives and sensitive to the patients' needs; the different levels must be well coordinated and clear referral criteria and competences must be established. (12).

RS of different types of studies 1+/2+

There is evidence of the benefits of PC (25-28) at home and in the hospitals and in PC units (*hospice*). Although the studies present some design problems, the results are coherent and show a consistent benefit in the satisfaction of the carers and a modest effect at result level on the patients (pain, symptom control, reduction of anxiety) (25-27).

The PC models where the interaction between the basic level and the support level pursue aid and not replacement are associated with greater satisfaction of PC professionals and an improvement in the result of the service offered by the system (29).

In a recent review (30) carried out in order to establish referral criteria between levels, it concludes that the support teams can provide the appropriate treatment for complex cases, whilst the involvement of the primary health care teams provides greater accessibility (for example, better understanding of non-cancer cases), more continuity in the care, greater number of deaths at home and a smaller number of visits to hospital emergency units. The review underlines health-care continuity as one of the main factors valued by patients and families that receive PC.

Qualitative research Q

The qualitative work carried out with patients and families indicates, too, that these perceive lack of continuity as a barrier that has a negative effect on their experiences.

There is evidence, too, both at home and hospital, of the benefits of coordination with PC teams in patients with more complex care needs (1; 30).

Expert opinion 4

The National Strategy recommends «establishing an organisation system that will guarantee coordination between the different health and social resources and foster integrated actions» (1).

Although there is no clear evidence about the best organisation model (12), most programmes contemplate several care levels, depending on the volume and complexity of the patient's problems (1; 30):

- The level of basic, primary or general PC, or palliative approach refers to the care that must be provided to all patients that require it in any care setting: primary health care, any hospital service (oncology, radiation therapy, internal medicine and other clinical services), emergency services, centres of social health, etc..
- The level of specific, secondary, specialised or advanced PC contemplates complex interventions that require specialised techniques or procedures.

Some authors call hospital care in PC units *third tier*.

Basic level

Expert opinion 4

The basic level should (12):

- Assess the patients' needs at different moments in time and in different care areas.
- Respond to these needs, in agreement with their own capacities regarding knowledge, skills, competences and resources.
- Know when to refer patients to other services.

Advanced level

The advanced level should:

- Provide care to patients with more complex and intensive health-care needs.
- Perform additional diagnosis tests or very specific treatments that need to be done in the hospital setting or treatments to cope with symptoms that are difficult to control.
- Attend to certain needs that are not necessary clinically complex, but that are social or family needs.

In our setting, centres for social health or specialised care units in PC can be:

- **Palliative care support teams:** They can intervene in the home or hospital setting and with different patterns, from advice to one-off, intermittent interventions or with shared responsibility in direct care. There are different home care models in Spain: Home Hospitalisation Units, Home Care Programme and Support Teams (PADES), Home Care Support Equipment (HCSE) and home teams of the Spanish Cancer Association (AECC), among others.

Mixed formulas can also be chosen, with teams that intervene in home and hospital settings.

- **Palliative Care Units:** These are specific PC hospitalisation units, attended by an interdisciplinary team. They can be located in acute, specific or social-health type hospitals. The units often also carry out outpatient and hospital support team work (1).

The way these two care levels are provided depends on the characteristics of the setting (rural, urban, etc.) and on available resources.

Expert opinion 4

A definition of the functions that each care field (primary health care, specialised care) and each level (basic or advanced) must carry out is essential, as well as the necessary qualifications, the way to coordinate between level and the necessary resources.

Recommendations

D	Palliative interventions should be based on the patient's and the family's needs more than on expected survival time.
D	All patients in end-of-life phase (EOL) should have access to a basic level of care in all care areas.
B	Health organisations should foster the training of their professionals to provide basic PC, regardless of the care area.
D	Service organisations should guarantee accessibility to specialised care when necessary.
B	PC at any level should preferably be provided by a suitable multi-disciplinary team.
B	Health organisations should define the functions they have to carry out and the training that the different service procurement levels should have in PC with respect to patients and their families.
B	Health organisations and the actual care services should guarantee coordination among the different services and care areas as well as continuity of care, 24 hours a day, 365 days a year.

4.4. Survival prediction

The questions that are going to be answered are:

- What is the validity of the prognosis scales to predict survival in patients in EOL?

Professionals attending to patient in EOL often have to answer the following question «How much time do I have left?». Predicting survival and informing the patient is a complicated process, which involves an individual assessment of the prognosis and adequate communication skills. Predicting survival is important to be able to provide patients and families with the required information, and to establish appropriate diagnosis and therapeutic plans (31). The way the prognosis is notified is just as important as its accuracy.

In order to improve diagnostic accuracy, different prognostic factors and prediction models have been evaluated. The latter (mainly developed for cancer) can be useful, always bearing in mind that their value is probabilistic (indicating average survivals) and that their application to an individual patient is more subject to uncertainty, which requires great caution when providing the information. It must also be taken into account that many instruments have not been validated in our setting and the impact of their use in clinical practice is unknown (32).

4.4.1. Survival prediction in cancer patients

One SR (33) explored the precision of the clinical evaluation of survival in patients with advanced cancer in a specialised PC context. Clinical prediction is an independent predictor of real survival, as it explains 51% of its variability. However, it is inaccurate and, in general, tends to overestimate survival. The prediction is more accurate when the survival time is less, and it also improves in patients with a low Karnofsky index. (<40).

SR of prognosis studies 2++

In another SR (34) the prognostic factors of survival were assessed in patients with advanced cancer (average survival of less than three months). The factors definitely associated with survival were: low functional status (Karnofsky), clinical estimation of survival, cognitive worsening, anorexia, dyspnoea, xerostomia, weight loss and dysphagia

SR of prognosis studies 2+

The classification of patients with advanced cancer into three groups made by Palliative Prognostic Score (PaP score) (35; 36) is acceptable. This classification depends on their probability of survival at 30 days, which is established with the following parameters: clinical prediction of survival, Karnofsky index, anorexia, dyspnoea, white blood cell count and lymphocyte percentage. It is not acceptable for patients with haematological tumours. It is carried out in the context of specialised care. It has also been validated in different populations (32). It is the recommended scale following the systematic review carried out by the European Association for Palliative Care (32).

Clinical prediction rules 2+

The Palliative Prognostic Index (PPI) (37) predicts survival at 3 and 6 weeks for different cut-off points. It requires greater validation.

Clinical prediction rules 2+

Clinical experience improves the prognostic accuracy, but it gets worse when the relationship between physician and patient is not very close. The quality of life scales can also be useful for survival prognosis (31).

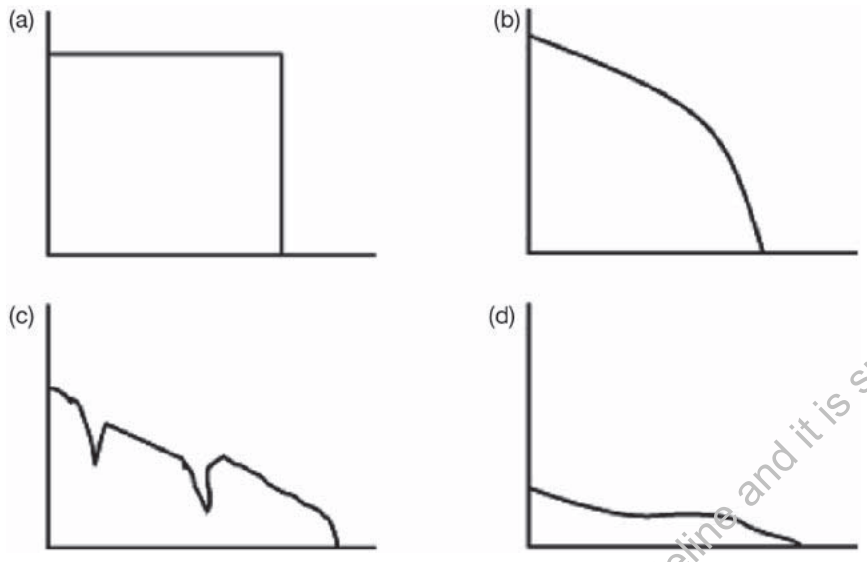
Expert opinion 4

4.4.2. Survival prediction in non-cancer patients

A recent SR (38) assessed the studies on survival predictors in patients over 65 years of age with non-malignant terminal illness. The generic prognosis models to estimate a survival of six months or less in patients without cancer have a low predictive value, which reflects the low predictability of non-malignant illnesses (figure 3).

Prognosis studies SR 2+

Figure 3. Dying Trajectory



Different trajectories of dying. On the y-axis, the state of health; on the x-axis, the time.

(a) Sudden Death, (b) Cancer Deaths, (c) Death from advanced non-oncological disease (COPD, heart failure, HIV-AIDS), (d) Death from dementia.

The classification made by the Walter scale (39) of the risk of mortality after one year in patients aged 70 and over after hospitalisation and based on six prognosis factors is acceptable: male gender, modified Katz index (40), comorbility (Charson index (41)), presence of cancer, creatinine >3 mg/dl, albumin <3-3,4 g/dl. It requires a more extensive validation.

The PaP is not sufficiently validated in non-cancer patient.

The CARING scale (42), applicable to all types of patients (cancer or non-cancer), developed in the United Status, seeks to select the PC candidate population from patients admitted to hospital. It is based on criteria that are simple to obtain, like the number of admissions due to neoplastic diseases or in an intensive care unit. The scale acceptably predicts the mortality one year after admission, but it need to be validated and reproduced in other contexts before proposing its use in our setting.

Clinical prediction rules 2+

The SUPPORT (43) and NHPCO (US National Hospice Palliative Care Organization) models (44), for patients with COPD, heart failure and terminal hepatic illness do not accurately estimate survival. The BODE index (45) uses the FEV, distance (in metres) covered in six minutes, the degree of dyspnoea and the Body Mass Index (BMI) (<21) to predict the risk of mortality from COPD. Its prediction is significantly better than the isolated FEV, but does not reach the acceptable prediction criteria proposed in the Coventry review (38), and requires a more extensive validation.

There are other studies not included in the Coventry SR (38) that are worthy of consideration, as they are based on variables that are simple to obtain, they provide an acceptable prediction and have extensive validation.

The Seattle Heart Failure Model, valid for outpatients and hospitalised patients with congestive heart failure (CCI) (46), is based on clinical parameters (age, gender, NYHA class, weight, blood pressure, presence of myocardial ischemia, medication used); analytical parameters (haemoglobin, % lymphocytes, uric acid, cholesterol and sodium), use of implantable devices and electrocardiograph (QRS > 120 sec). It predicts survival at one, two and five years, as well as the average age expectancy. It is validated in five cohorts of patients originating from RCT (randomised clinical trials). An online version can be used available at http://depts.washington.edu/shfm.

Clinical prediction rules 2+

In hepatic failure, the mathematical model MELD (Model for End Liver Disease) (47), based on values of creatinine, total bilirubin and INR, was created to select patients with hepatic cirrhosis and portal hypertension, candidates for placement of TIPS (Transjugular Intrahepatic Portosystemic Shunt), but it has been validated in different cohorts of patients with advanced chronic hepatopathies with an acceptable capacity to predict mortality at three months. The score is obtained with this formula: MELD Score = 9.57 Ln(Creat) + 3.78 Ln(Bili) + 11.2 Ln(INR) + 6.43 (calculator available at http://www.hepatitis.cl/meld.htm).

Until scales, which are simpler to obtain, have good predictive capacity and are validated in our setting, are obtained, some specific predictor variables can be used for some illnesses:

- In dementia: the functional state (value equal to 7C or over in the FAST, Functional Assessment Staging scale), dependence (ADL scale, Activities of Daily Living) or the medical history of complications.
- In COPD: age, FEV1 <30%, blood gas test, cor pulmonale with pulmonary hypertension, level of dyspnoea, capacity for exercise, St. George's quality of life questionnaire (SGRQ), etc.

For further information, consult appendix 2.

Summary of evidence

2++	The clinical estimation of survival is an important independent predictor of real survival in patients with advanced cancer, although it tends to overestimate it. The estimation is more precise when the survival time is less and in patients with a Karnofsky index of less than 40 (33).
4	Clinical experience improves the prognostic precision, but it worsens when the relationship between physician and patient is very close (31).
2+	The prognostic factors in patients with cancer associated with survival are: the functional state (Karnofsky), the clinical estimation of survival, cognitive deterioration, anorexia, dyspnoea, xerostomia, weight loss and dysphagia (34).

2+	The classification of patients with advanced cancer into three groups made by Palliative Prognostic Score (PaP score) (35; 36) is acceptable. It has been validated in different contexts, mainly in specialised PC units and oncology services. The scale is insufficiently validated for use in non-cancer patients (35; 36; 48).
2++	The generic prognostic models to estimate survival of six months or less in patients without cancer has a low predictive value, which reflects the low predictable course of non-malignant illnesses. Several specific prediction variables have been identified for some illnesses, which may help physicians identify older patients with a worse prognosis and with greater CP needs (38).
2+	In ICC patients and ejection fraction <30%, the Seattle Heart Failure Model acceptably predicts survival at one, two and five years (45).
2+	In patients with advanced hepatic disease, the MELD (Model for End Liver Disease) makes an acceptable prediction of survival at three months (47).
2+	The classification made by the Walter scale of the risk of mortality after one year in patients aged 70 and over after hospitalisation and based on six prognosis factors is acceptable: male gender, modified Katz index, comorbility (Charson index), cancer, creatinine >3 mg/dl, albumin <3-3,4 g/dl; but it requires further validation (39).

Recommendations

C	To estimate survival in patients with advanced cancer, elements other than clinical impression, should be taken into account, such as the presence of prognostic factors, the functional status (Karnofski) or the PaP prognostic scale (Palliative Prognostic Score). The latter is recommended within the context of specialised PC units or in oncology, as it has not been validated in other areas.
C	In non-cancer patients, the general survival predictive models require further validation. It is preferable to consider bad prognosis factors of each disease or validated scales (Seattle Heart Failure Model for ICC and MODEL for hepatic failure), always bearing uncertainty in mind and the less predictable trajectory of non-malignant diseases.
√	The way in which the prognosis is notified is just as important as its precision.
√	Validation of the different instruments in our setting is necessary, as well as the assessment of the impact of their use on clinical practice.

5. Information, communication and decision-making

The questions that are going to be answered are:

- How should the team attending to the patient and his or her family communicate?
- What must the communication training of the health professional working with patients in EOL be like?
- What legal regulations and ethical principles exist relating to communication with people in EOL and with his or her family in our setting?
- What are the decision-making elements in EOL?

5.1. Principles for adequate information and communication in palliative care

Interpersonal communication in the context of palliative care is the process that makes it easier for patients and carers to explore their problems and make decisions through interviews with the professionals responsible for their care (12).

5.1.1. Communications needs of patients and their families

In the Anglo-Saxon setting and in other countries of our environment, patients normally ask for detailed information about the diagnosis and the prognosis. This is less frequent in our setting. According to studies carried out in Spain, around 50 to 70% of cancer patients want to be informed about their diagnosis, but a substantial proportion of the patients (16 to 58%) and above all families (61 to 73%) prefer not to be told the diagnosis. Studies seem to indicate a progressive change in mindset towards a greater demand for information, above all in younger patients (12).

SR of different types of studies 3/Q

A recent SR (49) assessed studies on the preferences of patients with very advanced illnesses and those of their families in questions with respect to notifying the prognosis and to the end of life. The authors conclude that, in general, patients and carers of Anglo-Saxon/Northern origin demand greater levels of information, both with respect to the actual illness and to the symptoms, its management and also, about the life prognosis and to the different therapeutic options. The tendency detected in some studies of countries outside the Anglo-Saxon context (such as Spain and Greece) reveal that patients prefer less detailed information about the prognosis or other aspects related to the EOL.

In a comparative study carried out among patients and families in Canada and Spain at the start of care in PC units, significant differences were observed regarding the demands for information about the illness (type and prognosis) and management aspects (treatment administration) (50). Spanish patients expressed less desire to know the information, although mores so than their families. This discrepancy was not observed in the Canadian group.

Other factors related to less demand for information are noticed in the SR (49), such as advanced age and short survival expectancy. The review underlines that it is not possible to generalise about the information needs based on demographic or cultural characteristics. Health professionals are recommended to assess the information needs individually and continuously throughout time. Another peculiarity detected in the review is that, in general, as the illness advances, the patient has less need for information whilst the demand increases in the carers.

5.1.2. Communication Styles

SR of different types of studies 3/Q

With respect to the communication style, practically all the SR studies (49) originate from the Anglo-Saxon setting. Patients and families point out that information must be sincere, sensitive and with a realistic hope; that they want to feel that professionals showing empathy are actively listening to them, that they should use clear language and supply the information in small amounts. The conclusions coincided with the qualitative study carried out in our setting. With respect to whether the information should be given to the patient on his or her own or accompanied by another person, the results of the SR are variable and must be evaluated individually (49).

Other publications show conclusions along the same line. Patients consider that one of the basic attributes that a health professional should have is the «willingness to listen and explain» (51). Other studies highlight the importance granted by the carers of patients in EOL to the decision-making being shared and to the patient's relationship with the health professional being established in horizontal and participative conditions (52).

On the contrary, inefficient communication has been associated with therapeutic non-compliance and with an increase in patients' stress, as well as with dissatisfaction with the work and emotional wear and tear of the health professionals (51). Furthermore, lack of information, lies or hiding relevant information for a protective purpose may trigger other types of problems: the patient may receive contradictory messages from different professionals or may not be given the chance to express his or her fears and concerns. The patient's need for information must not be forgotten and his or her preferences in decision-making may change as the illness progresses, so a periodical evaluation is recommended.

5.1.3. Information methods

One SR (53) assessed some information methods, such as written information, audio or video material, etc. aimed at patients with recently diagnosed cancer and their families. The interventions studied had positive effects on knowledge and frequentation, symptom management, satisfaction, the use of services and the affective state. However, some of the interventions in specific patients had harmful effects. The review underlines that the methods must not be used uniformly, but rather, individual preferences for information must be taken into account.

SR of RCT 1+

5.1.4. Attitude of health professionals

The studies suggest that the interpretation made by the health professionals of the patients' preferences often differs from their wishes. In a survey on attitudes and beliefs carried out with PC specialists in Europe, Latin-America and Canada, the majority of clinicians stated that they would wish to be told the truth about their own terminal illness. However, 93% of the Canadian physicians, and only 25% of the European physicians and 18% of the Latin American physicians thought that the majority of their patients would wish to know the truth (54).

Descriptive study 3

On the other hand, one SR (47) confirms that clinicians tend to underestimate patients' information needs and to overestimate their degree of knowledge and understanding of the prognosis and of the aspects relating to the EOL and that of their carers.

SR of different types of studies 3/Q

5.1.5. Effects of effective communication

The research carried out suggests that efficient communication has an influence on the patients' health in different aspects such as the emotional state, the solution of symptoms, the functional state and pain (55). The appropriate exchange of information can improve patients' involvement in their care and adherence to treatments. It can reduce psychological distress and transmit realistic expectations (56). An appropriate communication process also helps patients and their families adapt to the new situations. It also helps them assimilate the illness and consider the different options (57). Offering patients the possibility of making shared decisions can reduce the symptoms of anxiety and depression (58).

SR of different types of studies 2+/3

5.1.6. Delivering bad news

Buckman calls «any information capable of drastically altering a patient's vision about his or her future» *bad news* both when the diagnosis of an illness considered a mortal illness is communicated and when informing about the failure of the curative therapeutics that are administered to the patient (59).

When delivering bad news, health professionals should bear in mind the barriers that may condition effective communication: deficit of skills to evaluate the information needs and to facilitate the participation of the patient and of his or her family in decision-making, tendency to interpret the patient's wishes and needs, the mistaken idea that «if the patient wants, he or she will ask», the feeling of being considered responsible for the failure of the cure, the belief that the information will produce greater harm to the patient or the uncertainty about certain aspects such as the patient's diagnosis or prognosis (12; 60-62).

There are different proposals for delivering bad news. The proposal of Rabow & McPhee (63) and the SPIKES protocol (64) are included in appendix 3.

5.2. Palliative care communication training

One SR (51), which included three RCTs performed with medical and nurse practitioners looking after cancer patients, evaluated the efficiency of communication training programmes. The interventions consisted in intensive courses (three days or by modules), and the results studied measured the changes in behaviour or in communication skills via objective and validated scales. These interventions seem to be effective in some areas: they improve communication skills (formulation of more focused open ended questions), they increase the expressions of empathy (answers that adapt better to the signals) and they provide a greater control of the clinical interview.

SR of RCT
1+

A subsequent study, with a four-day intervention organised into small groups and based on real scenarios with simulated patients, confirmed these findings (65).

Prospective study
2+

Communication training interventions benefit from subsequent refresher sessions (66; 67).

RCT
1+

5.3. Ethical and legal aspects of information and communication in palliative care

Access to the truth is a right that all patients have, as every person, with support and fully aware of the consequences, is entitled to decide on such important aspects of their lives as the health/illness process, or life or death (68). In this regard, honest communication is an ethical imperative for the health professional (53; 57) and it also involves respect for the wishes and values of the patients, in other words, of the principle of autonomy (57), permitting the care to be organised according to the patients' priorities and preferences and facilitating shared decision-making.

Legal regulation LG

The Spanish legislation covers these rights of patients. Thus, the General Law on Health established the right for patients and their families to receive «complete and continued, verbal and written information, about their process, including the diagnosis, prognosis and treatment alternatives». Chapter II of Law 41/2002, on the Patient's Autonomy includes the right that patients have with respect to health information, indicating that they are entitled to know all the available information about any action, and they also have the right of not to be informed. It stipulates that, as a general rule, the information will be verbal and it will be recorded on the medical history. This information will include the purpose and nature of each intervention, its risks and its consequences, at least. It must be true, understandable information, adapting to patients' needs, so that it can help them make their own decisions. It should be the physician responsible for the patient who guarantees compliance with the right to information. With respect to the family (art. 5), they can be informed insofar as the patient expressly or tacitly permits this.

Expert opinion 4

However, delivering bad news is one of the most difficult questions in PC and it is one of the aspects that generate the most conflicts in communication with patients and their families.

On the one hand, a physician or any other health professional who, faced with a fatal prognosis, insists on informing of everything, regardless of the patient's wishes, and who then also distances himself from that painful reality, abandoning him or her, subjects the patient to improper suffering (59). Informing patients, guaranteeing that they are not going to be abandoned, and in a context where they can express their concerns and fears, facilitates adequate communication and the emotional support they need.

On the other hand, hiding the diagnosis can possibly generate what is called a *conspiracy of silence* and which is defined as the implicit or explicit agreement by family, friends or professionals, to alter the information given to patients in order to hide the diagnosis or prognosis or seriousness of the situation from them (68). The conspiracy of silence makes it difficult for patients to adapt to their illness and prevents them from participating in the decision-making (69). On the other hand, patients, who often suspect they have a malignant illness (70), may appear fearful, anxious and confused when information is hidden from them (57). Managing this situation requires providing the main carer and the family with appropriate information and having good communication with them, trying to establish agreements (69).

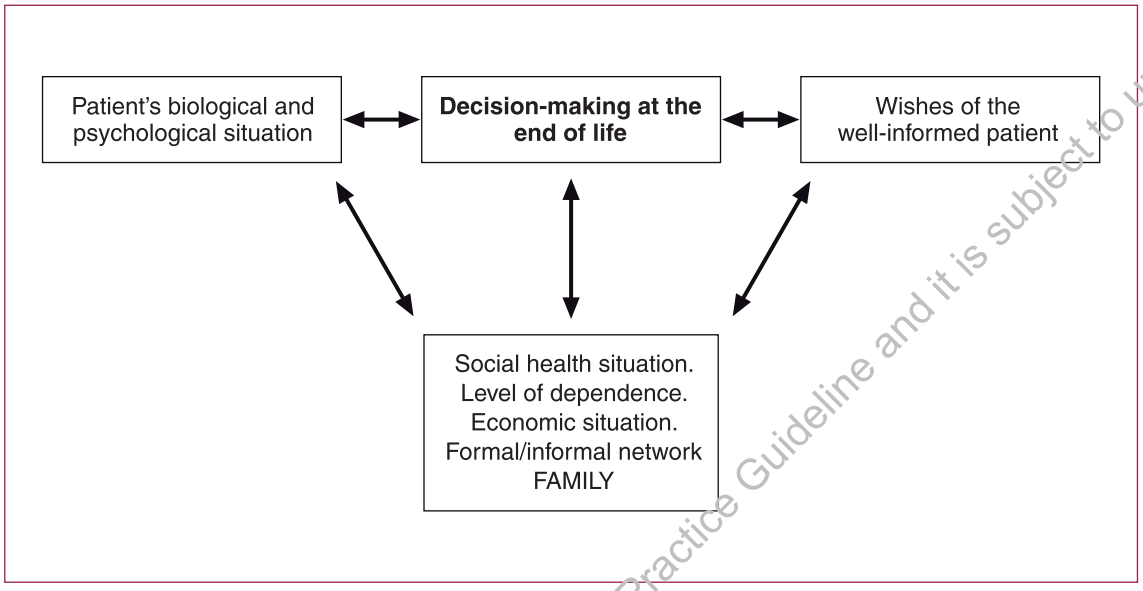
5.4. Decision-making elements

The people involved in the health relationship to make decisions in EOL must take both the patient's psychological and biological situation and the wishes of the correctly informed patient into consideration.

These aspects —*the patient's biological and psychological situation and his or her wishes*— are interrelated and are influenced by the family and social situation. The patient's level of physical or psychic dependence, his or her economic situation, the quality and quantity of support provided by the formal or informal

and the way the actual patient and his or her family live with the illness, may condition both the biological situation and the patient's wishes (71), as shown in figure 4.

Figure 4. Decision-making elements



When health professionals wish to determine the patient's situation in order to put forward decisions, they should ask some questions about the patient's life prognosis, his or her quality of life or social-health situation and, based on this, put forward the appropriateness or not of going deeper into the diagnosis techniques or more invasive treatments (cardiopulmonary reanimation, advanced vital signs support, surgery, chemotherapy, radiation therapy, artificial nutrition, etc.).

This evaluation should consider the following criteria: the proportionality, futility and quality of life. Sometimes, just by applying the treatments for a reasonable period of time and later assessing them, it will be possible to acknowledge if the patient reasonably responds to them.

The positive and the negative effects of the treatment are analysed through the proportionality criterion, as well as the burden the side effects may represent or the pain that may be generated. A diagnosis resource or a treatment is considered to be proportionate when it provides greater benefit for the patient (72). In this sense, it should be taken into account that the preservation of the patient's life is an obligation when the fact of living represents a benefit rather than a burden for the actual patient.

Futility has been invoked in the following clinical situations: cardiopulmonary reanimation, artificial maintenance of the vital functions when there is an irreversible loss of the superior brain functions (permanent vegetative state or deep dementia), aggressive treatment in terminal or dying patients, treatments that only offer a very low quality of life, especially if accompanied by great suffering, or if

there is no hope of doing without intensive care. In these circumstances, it is considered that treatment is futile when the benefits obtained occur in a percentage of below 1% - 5% of the patients treated (73).

With regards to the quality of life, it is the patient who can evaluate this best. If it is taken into account that what for one person may seem disproportionate or futile, may not seem so for another, it can be seen that, like the quality of life criterion, the criteria of proportionality and futility involve value judgements, complicating the debate about the usefulness or appropriateness or not of certain treatments at the end of life.

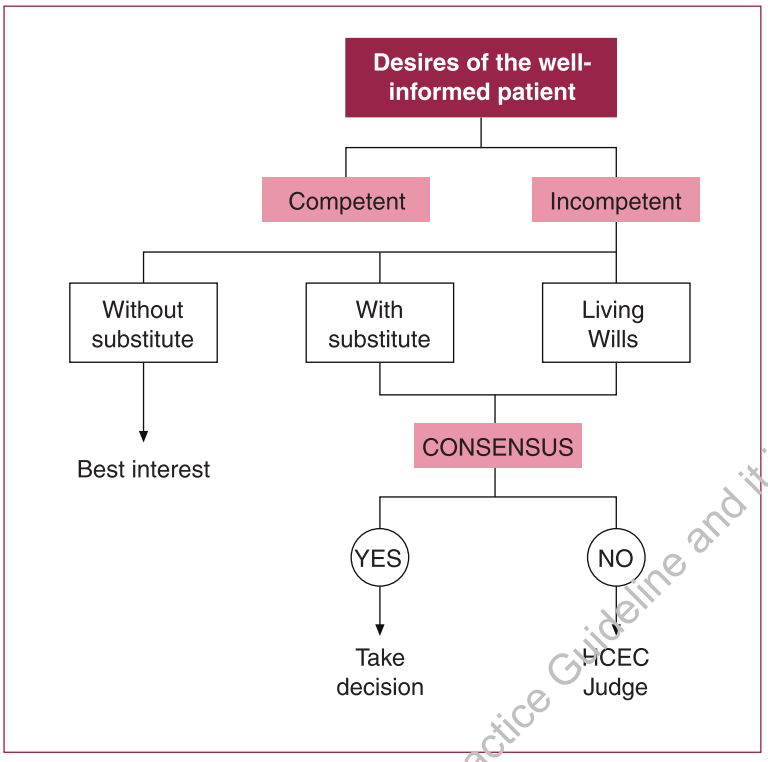
Having clarified the importance of subjectivity when managing criteria that will help up weigh up the efficiency of the treatments, it is essential to know the *patient's wishes,* as it is the sick person who must decide if he or she wishes the treatment proposed to be applied or not. Consequently, and as described, when reference has been made to the information and communication process, the importance of this process within the clinical relationship can be understood, as in this way the patient can make a clear judgement of the situation and can evaluate if the treatment advised is proportionate or not for him or her, and if the resulting quality of life levels are acceptable or do not meet the humanity and dignity requirements necessary to continue living.

Another basic aspect to recognise the patient's wishes is to determine his or her competence to make decisions. The assessment of competence is normally focused on the patient's mental capacity, above all on the psychological skills necessary to take a correct medical decision. Professionals should verify if patients have understood what has been explained to them and if they can make a decision about the treatment based on the information they have been given. The *consent* must be understood as a gradual and continual process through which an able and appropriately informed patient accepts or rejects being submitted to certain diagnosis and therapeutic procedures depending on his or her own values (74). A knowledge of the values that have formed the patient's life permits assessing the coherence of his or her decisions. This evaluation cannot be based on momentary knowledge of the patient. So, continuity in the care or the contribution of information by the general practitioner or the actual family provide the necessary data to evaluate this coherence.

Legislation LG

When the patient is incompetent, it must be determined if the incompetence is transitory or permanent, as well as its level. With respect to the information that must be provided in these cases, Law 41/2002 indicates that the patient will be informed even in case of incapacity, in a way that adapts to their possibilities of understanding. It then explains that the patient's legal representative must also be informed. Therefore, one of the tasks of the health professional will be to identify a substitute or representative for the patient in decision-making. In our normal practice, this is usually a family member. This person substitutes or represents the patient in the decisions, based on the best knowledge of his or her values and considering what best adapts to his or her interests (figure 5).

Figure 5. Decision-making in incompetent patients



When getting to know the values of incompetent patients, both Law 41/2002 and the different laws promulgated in different autonomous community contemplate *living wills* (LW) or *preliminary instructions* (PI). The legal development of the LW or PI varies in its content in the different autonomous communities (23).

Broadly speaking, the content of LWs is used so that any person can express their life goals and personal values that will help interpret the instructions and facilitate decision-making, on leaving a written record of their wishes with respect to medical actions in a situation where the circumstances that come together do not enable them to personally express their wishes. The LWs contemplate instructions about treatment – respect to a special, present or future, illness, or, in general, respect to medical interventions in agreement with best clinical practices- which will have to be respected by the physician or health team that looks after that person when he or she is in a situation whereby it is impossible for them to express their wishes. They appoint a representative who will be the valid spokesperson with the physician or health team and who will be empowered to interpret their values and instructions. They are formalised in writing, before a notary; before a civil servant; or before three witnesses who have reached the age of majority, who are fully able to take action and who are not linked to the executing person by marriage, free union or non-marital partnership, up to second degree relationship or any hereditary relationship. The executing person may amend them, substitute them or revoke them at any time, so long as he or she preserves their legal capacity and acts freely.

The problems are more complicated when patients have no family or do not have any LV document or any preliminary oral instruction. In these situations another criterion is used to take the decisions in incompetent patients. This criterion is called *best interest,* and it is determined by analysing risks and benefits according to the criteria of best clinical practice of the medical-scientific community and what society considers is best at that time.

Although the legal framework clarifies the decision-making process, the process is not free of problems, such as:

- The complexity of determining the competence of some patients, as there are no clear guidelines about how to do this correctly (75).
- The fluctuation of patients' preferences over time. A recent study (76), indicates that 35% of patients over 60 with cancer, heart failure or COPD showed fluctuations in their preferences when they had to decide on submitting themselves to aggressive or risky therapies aimed at prolonging their lives. Although variations in their state of health during the evolution of the illness can partly explain these fluctuations, the study suggests that these preferences are influenced by transitory factors, even in patients whose health is stable.

Cohort studies 2+

- The representatives' or close families' wishes may not be coherent with the wishes of the patients whom they represent. In the systematic review (77) which evaluated the precision of the representatives appointed by the patients or of close family members via hypothetical scenarios relating to interventions to prolong life, these did not appropriately reflect the patients' wishes in one third of the cases. The prediction also improved in the studies that evaluated the repercussion of previously discussing the values and preferences with family members. The authors mention that, despite these limitations, the predictions of the representatives or families are more accurate and therefore preferable to those of health professionals.

SR of cohort studies 2+

- The present-day health model is mainly paternalistically orientated, with enormous asymmetry in the roles of patients and professionals in decision-making.

Making the decision

Once all the steps indicated have been taken, the people involved in the clinical relationship will be in better conditions to make a decision. After the decision has been made, this should be communicated to the whole health team and to the patient's family. If there is consensus within the team of health professionals, and with the patient or his/her representative regarding the type of treatment to be followed, the decision will be taken. If there are difficulties to reach a consensus, either due to the difference in criteria among the actual professionals responsible for the patient, or to discrepancies with the patient or his/her representatives, the possibility of consulting the Health Care Ethics Committee (HCEC), a judge or other professionals should be evaluated, who will express their agreement with the patient or his/her representatives and can assume responsibility of the situation.

Legislation LG

In short, the elements to be taken into account in decision-making in the end-of-life phase are those given in table 1.

Table 1. Decision-making elements in EOL

1. Determination of the biological, psychological, social-health and family situation of the patient.
2. Assessment of treatments based on available scientific evidence, with the criteria of proportionality, futility and quality of life.
3. Consideration that decision-making is a gradual and continuous process which must include the participation of the patient or his/her representatives.
4. Guarantee that the communication process is adequate.
5. Supply of complete information, including available therapeutic options, their benefits, as well as expected risks and disadvantages.
6. Assessment of the patient's competence.
7. In the case of a competent patient, confirmation of his/her wishes and preferences; it is advisable to share the information and decision with the family.
8. In the case of a patient who is not competent to take a certain decision, the following options, in the order indicated, should be considered:
   a) Preliminary guidelines if there are any, consulting with the National Registry of Preliminary Instructions or the registries of the autonomous community where the patient resides.
   b) Wishes previously expressed by the patient and included in his/her medical history by the general practitioner or the hospital specialist physicians, if any.
   c) Legal representative.
   d) Closest family in charge.
9. If the health professional has doubts about the decision to be taken (appropriateness of the options proposed, patient's competence, discrepancies with the representative, etc.), the evaluation by other expert professionals or by health care ethics committees is recommended.
10. Inform the health team of the decision.
11. Record the decision-making process in the medical history.
12. Regulation framework (appendix 4).

Summary of evidence

LG	Law 41/2002 includes the patient's right to be informed and his/her autonomy for taking decisions about his/her health. It establishes the patient as the owner of the right for information, and for this to be transmitted verbally, with written record in the medical history. It also contemplates the right to not be informed, if the patient so wishes or due to therapeutic need. If the patient is not competent to take a decision, consent by representation rules.
LG	Patients are entitled to receive complete and continued, verbal and written information about their process, including the diagnosis, prognosis and treatment alternatives. The family may be informed insofar as the patient expressly or tacitly permits this.
LG	The content of living wills (LW) or preliminary guidelines (PG) is used so that any person can express their life goals and personal values that will help interpret the instructions and facilitate the decision-making, on leaving a written record of their wishes about medical actions in a situation where the circumstances that come together do not enable them to personally express their wishes. The regulatory development of Law 41/2002 on LV/PG varies according to the different Autonomous Communities.
3	The desire for information is influenced by factors such as cultural context (50), age or survival expectation; but it is not possible to generalise. Demands for information by patients decrease as the illness advances, whilst the demands by carers increase. Patients and families emphasise that the information must be sincere, sensitive and with a margin of hope; and that they wish to feel that they are being actively listened to by professionals who show empathy. They also want the information to be given clearly and gradually (49).

2+	Efficient communication affects the patients' health, acting on aspects such as emotional state, solution of symptoms, functionality and pain (55).
3	Communication may improve the patients' involvement in the care, reducing psychological distress and transmitting realistic expectations (56).
3	Health professionals tend to underestimate the patients' wishes to be informed and share decisions (54; 57; 78).
1+	The information methods aimed at patients with recently diagnosed cancer and their families (written information, audio or video material, etc.) have positive effects on some variables (the knowledge of the illness, management of symptoms, satisfaction or use of services). Some interventions in specific patients may have harmful effects (53).
1++	Intensive training programmes, with role-playing techniques or simulated patients, are effective for improving the communication skills of health professionals who care for patients with cancer (51; 65).
1+	Organised training interventions on communication benefit from subsequent refresher sessions (66; 67).
2+	The patients' preferences related to the therapeutic decisions can fluctuate with time (76).
2++	The decisions of representatives or close family members may not coincide with the wishes of the patients whom they represent (77).

Recommendations

C	Health professionals should have the necessary skills to effectively communicate with patients and carers and should receive adequate training in this regard.
√	The information and communication should be based on the preferences expressed by the patients. Health professionals should avoid interpreting their desires.
D	It is important for health professionals to explicitly show their willingness to listen and inform.
B	Patients' needs for information and preferences must be evaluated on a regular basis.
D	Relevant news, such as the diagnosis, should not be delayed and each patient's desire for information must be respected individually (including the wish to not be informed). They should be informed sincerely, sensitively and with a margin of hope. This type of information must be provided in a quiet, comfortable place, with privacy and without interruptions.
B	Verbal information can be accompanied by other reinforcement information methods such as written information. The methods should be based on individual preferences.
B	Health organisations should give professionals working with patients who require PC the possibility of receiving suitable training in communication skills. The training should be intensive, based on real scenarios and with subsequent refresher sessions.

D	The participation of patients and carers in decision-making at the end of life should be fostered, through suitably trained professionals and respecting people's wishes not to take part in the decisions.
D	Professionals who participate in decision-making must provide clear and sufficient information, letting the patient and his or her relations express their doubts and fears, solving their questions and providing the necessary time for reflection.
D	Clinics should make decision-making easy when faced with ethical dilemmas in EOL (limitation of therapeutic effort, food and hydration, sedation, etc.) bearing in mind the values and preferences of the patient and his or her family.
D	If the patient is not able to make decisions, the following options should be considered, in the order in which they are presented: a) Preliminary guidelines, if any. b) Desires expressed by the patient and included in his or her clinical records, if any. c) Legal representative. d) Closest relations in charge.
D	It is advisable to inform the team of the decisions adopted and record the process in the clinical records.
D	If there are doubts during the decision-making process, a request for advice from experts may be indicated (other professionals, Healthcare Ethics Committee, etc.).

6. Symptom Control

6.1. Introduction

The questions that are going to be answered are:

- What is the prevalence of the different symptoms in patients in EOL?
- How valid are the scales that evaluate the intensity of symptoms in patients in EOL?
- How should drugs be used in palliative care?

6.1.1. General principles for symptom control

Patients in EOL may present multiple symptoms, depending on the nature and state of their illness. In the case of patients with cancer, the location of the tumour, its degree, local extension and metastasis determine the symptoms.

National studies on prevalence of symptoms refer to cancer patients above all (19). In these series, pain, asthenia and anorexia appear in more than 70% of the patients.

The studies on prevalence of symptoms in EOL patients present a series of problems that mean they are difficult to compare: variability in the definition of symptoms, use of different definitions and scales (some not validated), stage of the illness (situation of agony, for example), presence of cancer, type of professional collecting the information, field of care (specialised or primary health care unit), etc.

SR of prevalence studies 3

A recent SR (79) studied the prevalence of symptoms in cancer and non-cancer patients (see table 2), classifying the 11 most frequent symptoms. Pain appears very frequently in all types of patients.

Table 2. Prevalence of symptoms according to type of patient in PC

Symptoms*	Cancer	HIV-AIDS	Cardiac insufficiency	COP COPD	Renal illness
Pain	35%-96% N = 10.379	63%-80% N = 942	41%-77% N = 882	34%-77% N = 372	47%-50% N = 370
Depression	3%-77% N = 4.378	10%-82% N = 616	9%-36% N = 80	37%-71% N = 150	5%-60% N = 956
Anxiety	13%-79% N = 3.274	8%-34% N = 346	49% N = 80	51%-75% N = 1.008	39%-70% N = 72
Confusion	6%-93% N = 9.154	30%-65% N = ?	18%-32% N = 343	18%-33% N = 309	—
Asthenia	32%-90% N = 2.888	54%-85% N = 1.435	69%-82% N = 409	68%-80% N = 285	73%-87% N = 116
Dyspnoea	10%-70% N = 10.029	11%-62% N = 504	60%-88% N = 948	90%-95% N = 372	11%-62% N = 334
Insomnia	9%-69% N = 5.606	74% N = 504	36%-48% N = 146	55%-65% N = 150	31%-71% N = 351
Nausea	6%-68% N = 9.140	43%-49% N = 689	17%-48% N = 146		30%-43% N = 362
Constipation	23%-65% N = 7.602	34%-35% N = 689	38%-42% N = 80	27%-44% N = 150	29%-70% N = 483
Diarrhoea	3%-29% N = 3.392	30%-90% N = 504	12% N = 80	—	21% N = 19
Anorexia	30%-92% N = 9.113	51% N = 504	21%-41% N = 146	35%-67% N = 150	25%-64% N = 395

* Percentage and total number of patients assessed for each symptom.

The assessment of the symptoms, as commented in the introduction of this CPG, has to be done globally in the context where the care if provided and bearing in mind its repercussions on the person and on the family environment. It is important to point out that the evaluation of the importance of the symptoms may differ between the person suffering and the professionals that care for them (80).

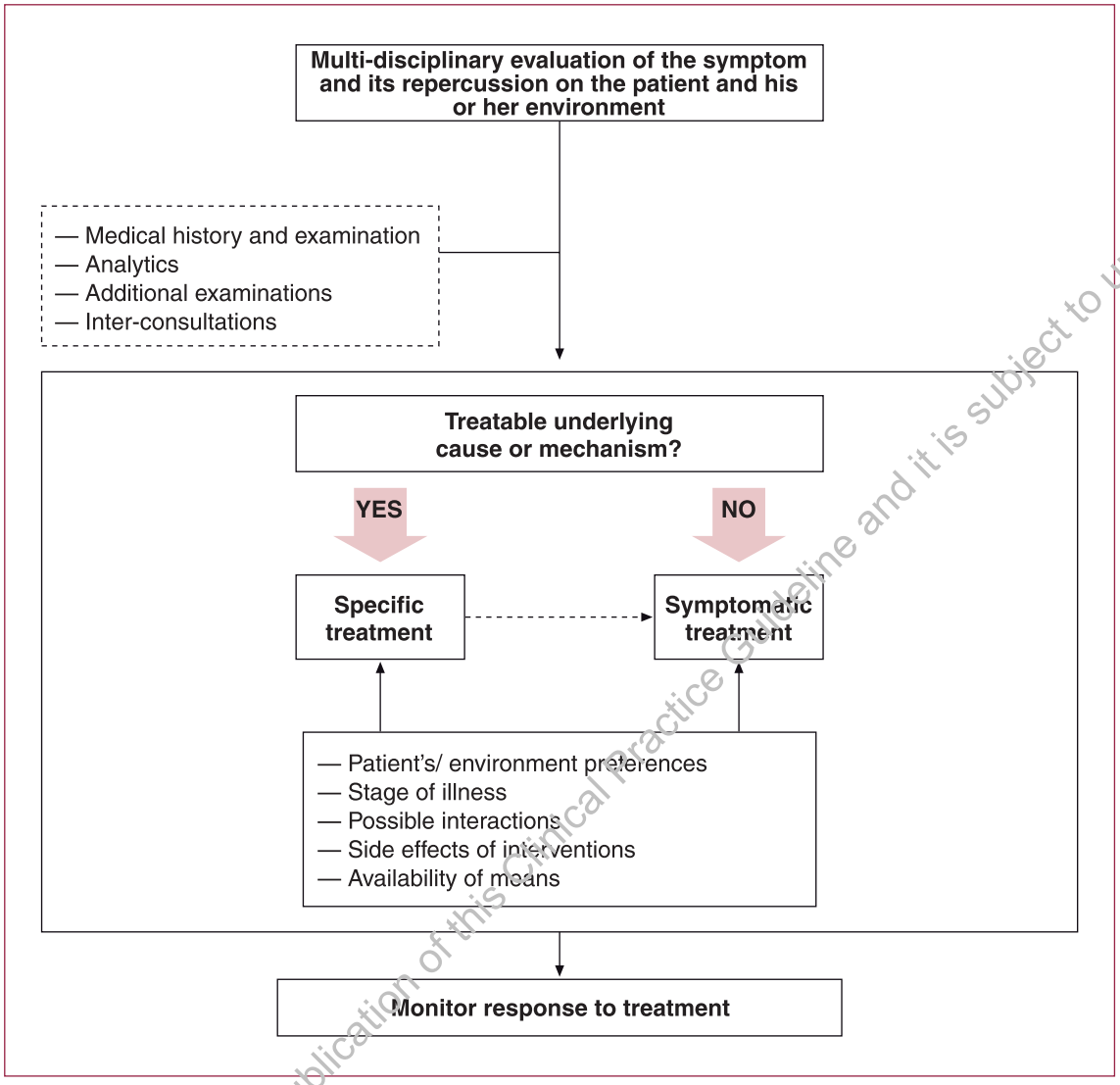
The evaluation must be multidisciplinary. There is a lot of literature that shows that physicians (oncologists, general practitioners, specialised unit physicians, etc.) evaluate the intensity of their patients' symptoms more inaccurately manner other professionals, nursing staff or ancillary staff.

The way in which the symptoms are compiled is important. The *intentional search* for symptoms via questions that address what concerns or bothers the patients may favour a better evaluation of the symptoms as a whole.

Symptoms change over time, due to the evolution of the illness, to the adverse effects of the therapies used (surgery, radiation therapy, chemotherapy), to the response to the palliative support of the team and to the actual experiences of the patient and his or her carer. All of this determines that the constant assessment and re-assessment of patients and their environment is a need and an essential feature of PC.

Figure 6 shows the general approach of the symptoms.

Figure 6. Algorithm of the treatment of symptoms



6.1.2. Evaluation of symptoms. Use of scales

The use of validated scales can be a useful strategy to standardise the assessment of symptoms and monitor the response objectively. This practice, demandable in clinical trials on treatments in PC, is not carried out in our setting as a general rule. The proliferation of instruments, the lack of validation of many of them and, above all, the lack of studies on their real impact may explain this fact.

SR of questionnaire validation studies 3

A recent quality SR assessed 21 symptom measurement instruments on patients with cancer (81). The review did not include scales that measured one single symptom, quality of life instruments or instruments that assessed the tumour response. The MSAS, Rotterdam Symptom Checklist, Worthing Chemotherapy Questionnaire, Oncology Treatment Toxicity Scale and the Computerized Symptom Assessment Instrument were appropriate for the initial evaluation and

for the follow-up. Other instruments appropriate for the follow-up were: MDASI; ESAS (Edmonton), SDS CAMPAS-R and Condensed MSAS. Of the instruments with five or less symptoms, HADS, Index of Nausea and Vomiting, and MANE were appropriate for certain symptoms or toxicity. The Symptom Monitor, The Camberra Symptom Score Card, Pain and Symptom Assessment Record, The Symptom Reporting Tool, and The Symptom Experience Scale require additional assessment. The evaluation of the symptoms by close friends is important in incompetent patients, but the reliability decreases, especially when dealing with psychosocial symptoms. The impact of the use of these scales has not been assessed in clinical practice.

The Rotterdam Symptom Checklist scale has been validated in Spanish and can be used in the research context or in studies on the assessment of the impact of PC (16). The ESAS scale (Edmonton Symptom Assessment System) (82) is more appropriate for clinical use due to its simplicity. This instrument is currently in a validation phase in Spain (83). For further information see appendix 2.

6.1.3. Use of drugs for symptom treatment in PC

Expert opinion 4

The principles for effectively controlling symptoms include (84):

- Preparation of a medical history and detailed examination that permit diagnosing the underlying mechanism or cause of each symptom.
- Personalised treatment.
- Treatment of reversible causes.
- Inform patient and his or her family.
- Evaluation of treatment options, both pharmacological and non-pharmacological.
- Simplification of treatment patterns.
- Monitoring of response.

The most commonly used drugs in PC, their dosage and relevant information are enclosed in appendix 5 (handbook, by symptoms and by drugs).

The use of drugs in PC has some special characteristics that must be taken into account (84). Patients with an advanced or terminal illness form an especially vulnerable population. Their environment and the different psychological factors may have a great influence on their physical wellbeing and on their response to a pharmacological treatment. At times this response will be unpredictable.

These patients are often elderly, fragile or with multi-organ affectation, as well as poly-medicated, with the subsequent risk of interactions and iatrogenia.

The challenge for professionals and carers consists in treating the symptoms effectively, keeping the patient as comfortable as possible and minimising adverse effects and disadvantages of the treatment or the very complex guidelines.

Another frequent problem in PC is the use of drugs in indications or conditions for use that differ from those approved in the prospectus. In the United Kingdom this affects about 15% of the prescriptions made in PC units (84).

When prescribing a drug in unauthorised indications or conditions for use, the following must be considered:

- The risk-benefit balance for the patient.
- The strength of the evidence that supports it use.
- The availability of alternative drugs or routes and their advantages and disadvantages.

To consult information on legal aspects, see appendix 4.

6.1.4. Drug administration routes in PC

The choice of the administration route depends on factors related to the patient, the drug and organisational type factors (availability of formulations, human resources, etc.).

The main administration route in PC is oral (liquid or solid forms), as it is a simple, non-invasive and acceptable route for patients.

Another alternative for the use of analgesic drugs is transdermal route, available only for fentanyl and buprenorphine for the moment.

The administration route for some drugs, such as buprenorphine, can be sublingual.

Subcutaneous route (SC) is used quite often to control symptoms as an alternative to the parenteral route (intramuscular or endovenous) when the oral route is not possible. The SC route is easy to access, it is tolerated well and does not require hospitalisation. It is used in palliative medicine both to administer drugs and to hydrate patients. The use of infusers also permits mixing drugs and administering them at the same time.

The lack of authorisation to use many commonly-used drugs by this route is a barrier for the use of the SC route. There is a time difference between the updating of the technical data sheets and the use of this route in agreement with the patient's best interest. So it is important to review the evidence about drugs used frequently by SC route.

SR of different types of study 1+/2+/3

One SR examined the evidence of administering drugs and fluids by SC route in older people. The majority of the drugs were used in the PC context. The indication for morphine and hydration is approved and is backed by extensive evidence. Some non-authorised drugs have good evidence (RCT or cohort or non-randomised controlled experimental studies) by SC route, including: butylscopolamine, ceftriaxone, chlorpromazine, fentanyl, hydromorphone and pethidine. Other drugs that have observational studies (controlled studies with possibility of bias, retrospective studies or case series) are: amikacine, buprenorphine, clodronate, gentamicin, ketorolace, metadone and midazolam. No studies were found

for atropine, haloperidol, levomepromazine, metoclopramide and diazepam, but there are non-systematic reviews that supported their use. No information was found on the use of clonazepam, clorazepate, furosemide, lorazepam and methylprednisolone. The reviewers conclude that studies must be carried out with frequently used drugs by SC route and that the laboratories should register this route if there are sufficient data (85).

For further information on the administration of drugs by SC route and the compatibility of mixtures, see appendix 6, as well as at http://www.pallcare.info.

Summary of evidence

3	The scales, MSAS, Rotterdam Symptom Checklist, Worthing Chemotherapy Questionnaire, Oncology Treatment Toxicity Scale and The Computerized Symptom Assessment Instrument are appropriate for the initial evaluation and follow-up. The MDASI; ESAS (Edmonton), SDS CAMPAS-R and Condensed MSAS scales are appropriate for the follow-up (81; 82).

Recommendations

D	The evaluation of symptoms of the EOL patient must be multidisciplinary, individualised, adapted to the patient and his or her family and continued in time.
D	If the use of symptom evaluation scales is chosen, the use of validated instruments is recommended. The ESAS scale can be used in our setting. The Rotterdam Symptom Checklist scale (validated in Spanish language) can be used in the research context or in studies on the assessment of the impact of PC.
D	The principles for effective symptom control include a personalised evaluation and, if possible, the treatment of the aetiology or mechanism that underlines each symptom; an assessment of the pharmacological and non-pharmacological treatments available; the choice of the most simple, effective and convenient treatment guideline; information to the patient and his or her family on available options, and the consideration of their preferences.
D	The preferential administration route must be oral. When the oral route is not possible, the subcutaneous route should be used. In some cases (fentanyl and buprenorphine) the transdermal route method can be used.

6.2. Pain Treatment

The questions that are going to be answered are:

- What is the prevalence of pain in EOL?
- How valid are the different scales for assessing pain?
- How efficient are the different analgesics (simple analgesics, NSAID, combinations of the above, opioids, etc.) and of adjuvant drugs in pain?
- How effective are the different opioids for breakthrough pain?
- What is the analgesic effectiveness of radiation therapy, palliative chemotherapy, bisphosphonates and calcitonin in cancer patients with bone metastasis?
- How effective are drugs in treating neuropathic pain of people in EOL?

6.2.1. Introduction

The International Association for the Study of Pain (IASP) defines *pain* as «an unpleasant sensory and emotional experience associated with actual or potential tissue damage» (86).

Pain is one of the most frequent symptoms in patients in EOL. It can affect up to 96% of patients with cancer (79).

Patients may have pain due to their illness (tumour infiltration, nervous lesions); as a result of some treatments (surgery, chemotherapy, diagnostic techniques), or related to their situation of immobility and general weakness (bone pains, ulcers, zoster herpes, etc.). One must not forget other possible causes of pain not directly related to the patient's illness (osteoarthritis, etc.).

6.2.2. General principles for pain treatment in PC

Pain in patients in PC represents something more than a nociceptive sensation and includes aspects that have to do with the human conditions, such as personality, affectivity and emotions, and psychosocial relations (87).

The multi-dimensional nature of pain in PC requires a multifactor intervention that includes pharmacological, psychotherapeutic and rehabilitating measures, among others. The psychic and physical aspects of pain are closely related. The psychosocial treatments aimed at solving variables of the psychological sphere improve pain whilst treatment that addresses nociception has beneficial psychological effects (87). Some authors have proposed the concept of *total pain* to refer to the sum of the nociceptive sensation together with psychological, social and spiritual aspects of each person (87).

Professionals caring for patients in PC have to bear this fact in mind, which explains the variability in the analgesic response to pharmacological and non-

pharmacological treatments. Partial approaches related to the person with pain can explain many treatment failures (87).

Communication with patients and their families is decisive for treatment success. If the information provided about the pain adapts to each situation and shows how to deal with it, involving the patient, there will be a better response to the treatment (88).

Before starting analgesic treatment plan an integral assessment of the patient must be carried out, bearing in mind his or her environment. Table 3 includes the general principles that must guideline the action of a professional team.

The intensity of the pain can be assessed using a validated scale. Many different instruments have been used until now. Carr (89), in his systematic review, found 25 different scales, applying the criterion that they were used in at least five different RCTs. The recent CPG by SIGN (88), based on a specific European consensus (90) on pain scales, recommends the use of visual analogue scales (VAS), numerical scales or verbal pain classification scales.

SR of questionnaire validation studies 3

Table 3. General principles to care for patients with pain in EOL.

- Assess the pain in detail: its intensity, causes, chronology and repercussions on patients and their families.
- Continuously re-assess the analgesic response, as well as the appearance of side effects of the medication.
- Approach the person with pain and his or her environment via psychosocial techniques and adequate analgesic treatments.
- Start with the analgesic step that best adapts to the type and intensity of pain (possibility of associating adjuvant treatments).
- Adequately treat breakthrough pain.
- Not use powerful and weak opioids together.
- Prepare for possible side effects of the drugs with preventive measures.
- Instruct patients and their families on the steps to follow in the case of breakthrough pain, insufficient analgesic response or appearance of side effects.
- Deliver clear instructions about how to contact the professional team caring for the patient in case of doubts or problems with the treatment.
- Give priority to the oral route for administering analgesics.
- Have criteria on the administration of analgesics.

The specific questionnaire, Brief Pain Inventory (BPI) in patients with neoplasia caused pain is validated in Spanish and includes two dimensions: intensity of the pain and interference in activities; each one of them is measured by a numerical scale from 1 to 10 (see appendix 2).

In the case of cognitive impairment, a recent SR (91) concluded that the scales, PACSLAC (Pain Assessment Checklist for Seniors with Limited Ability to Communicate) and DOLOPLUS 2 are the most appropriate in this situation. However, these scales are not validated for the moment in Spanish. These scales are based on observing the behaviour of the patient throughout a short period of time and on the response to the application of care (cures, mobilisations, etc.).

6.2.3. Classification of pain

Depending on the duration:

- Acute: produced by somatic or visceral nociceptive stimulations of abrupt onset and of short duration.
- Chronic: persisting pain, whatever its intensity, that lasts for more than one month.
- Breakthrough: pain of a moderate or intense intensity that appears over chronic pain. It can start unexpectedly or in a foreseeable manner (triggered by certain manoeuvres known by the patient).

According to its physiopathology:

- Somatic pain: produced by the stimulation of pain receptors in deep muscular-skeletal and surface skin structures. For example, metastatic bone pain.
- Visceral pain: caused by infiltration, distension or compression of organs within the chest or abdominal cavities. It is often associated with nausea, vomiting and perspiration. It can also produce referred pain in places other than the organ where it originates.
- Neuropathic pain: caused by direct lesion of nervous structures, either by direct tumour invasion, as a result of chemotherapy or by infections in a weakened patient (zoster herpes, etc.). The patient describes it as unpleasant, burning or shooting, or as a feeling of numbness, tingling, tautness, itchiness or pressure. It can become difficult to control as it responds badly to normal analgesics.
- Mixed: coexistence of several of the previous mechanisms in one same patient.

6.2.4. Efficiency of pharmacological treatment

Despite the high prevalence of pain in patients in EOL, especially in cancer patients, the results on the efficiency of analgesic treatment pose difficulties for their application in clinical medicine. The RCTs collected in different SRs have problems of validity and applicability. The studies are based on few patients, they are carried out for short periods of time, with single doses of drugs on many occasions, or using different ways of assessing the efficiency, so some results must be taken with caution. In most of the Cochrane SR it is not possible to group the results together in the form of a meta-analysis due to the heterogeneity (92-94).

The WHO analgesic ladder has been applied universally, although its proposals have not been assessed via RCT (88). However, a high percentage of pain relief is known to be achieved with its use. Jadad (95), based on prospective and retrospective studies without a control group, found that pain relief was adequate in between 69% and 100% of the cases. Another more recent review, with a larger number of studies, placed these percentages at between 45% and 100% (96). This CPG proposed basing analgesic treatment on the analgesic ladder of the WHO (see table 4).

Some authors propose adding a fourth step to the analgesic ladder of the WHO (97). This last step would be added in the case of persistence of the pain despite the correct use of the ladder, including the use of the subcutaneous route and of adjuvants. It would include instrumental techniques, such as the epidural administration of opioids, sympathetic blockages and other surgical analgesia techniques.

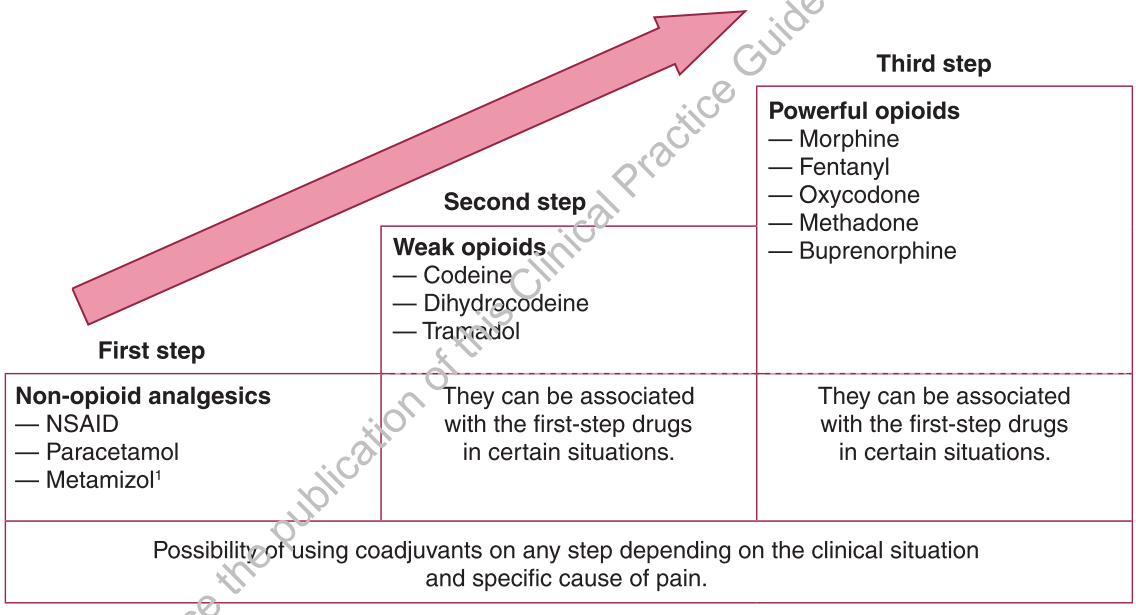
Expert opinion 4

The epidural administration of analgesics is quite a controversial technique. This administration method has not been sufficient assessed until recently (98). A first trial was published in 2002 (99) on cancer patients with refractory pain, on whom the spinal administration of morphine was efficient. This is a technique that can be evaluated in these cases (89; 100).

RCT 1+

These measures must be considered in selected patients and require the participation of specialised units, such as pain units. As indicated in the introduction, the assessment of its effectiveness is not the aim of this CPG.

Table 4. WHO's modified analgesic ladder



[1] Dypirone.

First step: this corresponds to non-opioid analgesics (NSAID, metamizol and paracetamol). The NSAIDs and the paracetamol have proved to be efficient with respect to placebo (92). No significant differences have been found between the different NSAIDs (92).

Second step: this corresponds to weak opioids; in our setting, codeine, dihydrocodeine and tramadol (101). The presentations of dihydrocodeine available in Spain do not adapt well to the analgesic doses.

There is widespread agreement on the possibility of associating first-step drugs with drugs from the following steps. However, the SR that studies the role

of paracetamol and NSAIDs (92) associated with opioids did not find any data either in favour or against the association. The characteristics of the pain and a meticulous assessment of each case determine the decision on the use of this association. NSAIDs are the first option in bone aetiology pain, as is the case of metastasis.

Third step: this is comprised of powerful opioids. The drug of choice is morphine, which can be used orally both rapid release (solution or tablets) and delayed release, by IM, IV or subcutaneous route (with possibility of using it in infusion pumps).

Oral morphine must be administered at the onset every four hours until adequate analgesia is achieved. Then, it can be changed to the equivalent dosage of delayed morphine in two doses. If adequate analgesia is not achieved, increases in dosage of 25% to 50% are necessary. In situations of stable pain, the use of delayed 24-hour presentation can be posed (88). A more detailed explanation about practical aspects of the use of opioids is given in appendix 7.

CPG 4

Methadone was compared with morphine in a SR and the efficiency was similar (93). This SR included RCTs of short duration and with different dosage patterns.

SR of RCT 1+

Methadone has a long average life, with risk of accumulation and very variable response, making dosage difficult. Oxycodone has no advantages over oral morphine as an opioid of first choice (102).

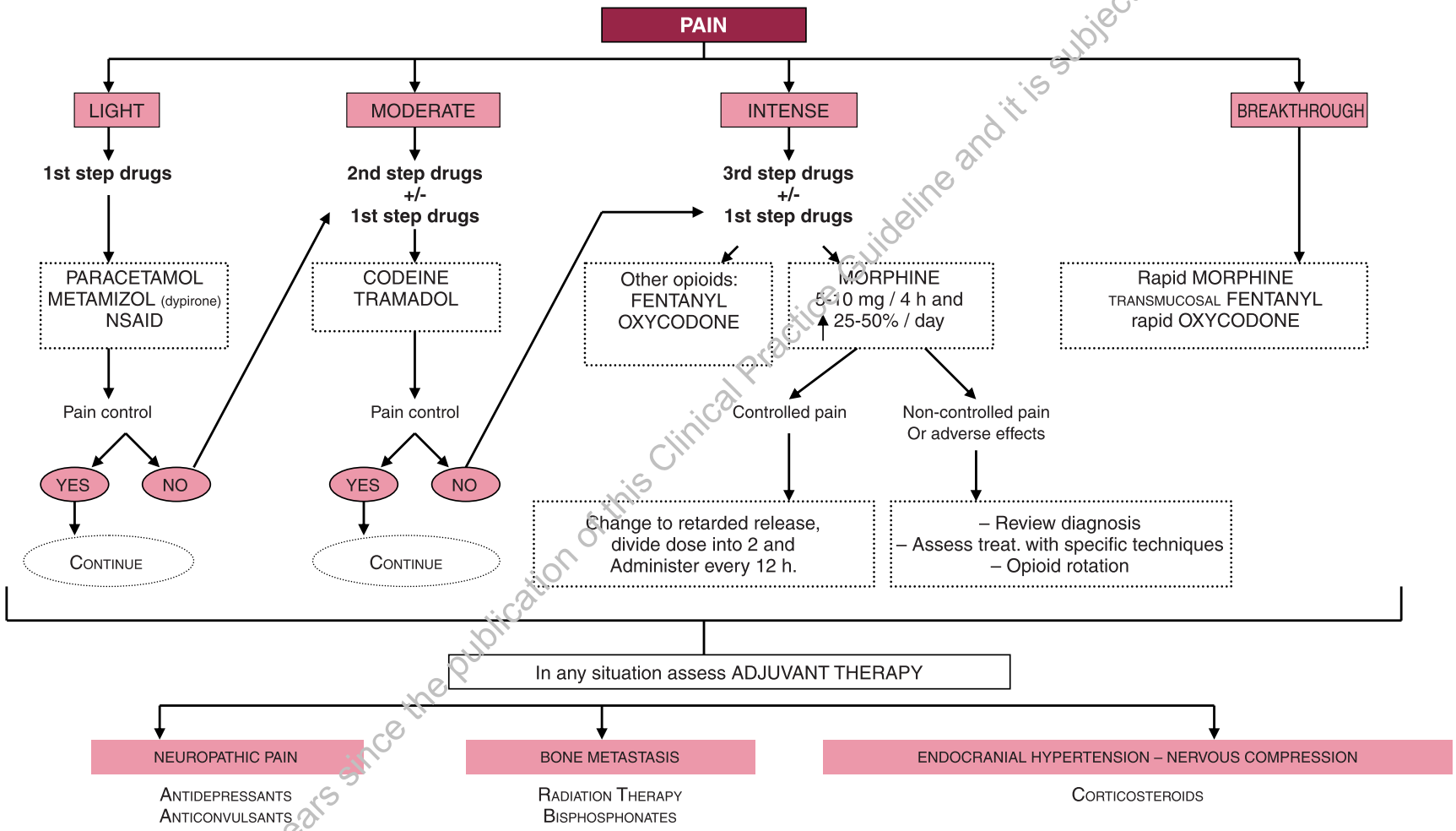
Fentanyl is not more efficient than oral morphine (94). It has the advantage of administration in the form of transdermal patches, which permit its use in case of swallowing difficulties (although it has not been assessed in this case compared with subcutaneous morphine), problems of compliance or due to patients' preferences. Its effect lasts for 72 hours; this makes it difficult to adjust doses, so it is not recommended in the case of unstable pain. It should not be started to be used during the last days of life, either (see appendix 7).

ECA 1+

Buprenorphine can be administered by oral or parenteral route and also by transdermal administration. Its effect by this route also lasts for 72 hours. There is less evidence about its use and it has not been assessed with respect to other opioids.

Figure 7 includes a summary of the use of the analgesic ladder during care of patients with pain in PC.

Figure 7. Algorithm for treatment of pain in PC



Side effect of opioids

The stimulation of opioid receptors is the cause of their systemic effects. Some of the side effects, such as respiratory depression or dizziness, disappear when tolerance to the drug appears. Others, such as constipation, persist during the treatment.

In one SR (103) on the adverse effects of opioids in non-malignant chronic pain, 25% of the patients suffered from a dry mouth; 21%, nausea and 15%, constipation. 22% of the patients abandoned the treatment due to its adverse effects.

In the population with malignant chronic pain, the incidence of adverse effects is greater. Table 5 sums up the most frequent side effects of opioids (104; 105).

Table 5. Side effects of opioids

	Symptoms	% Incidence
Gastrointestinal	Nausea, vomiting Constipation	15-30 40-70
Autonomic nervous system	Xerostomia, urinary retention, postural hypotension	No data
Central nervous system	Sedation, myoclonus cognitive impairment, hallucinations, delirium, hyperalgesia, convulsions	20-60 No data
Skin	Itchiness Hyperperspiration	2-10 No data

Possible therapeutic strategies to manage the adverse effects of opioids include: reduction of the dosage or suppression of the drug, change of administration route, opioid rotation and symptomatic treatment of the adverse effects. The first of these can be efficient so long as alternative analgesia is used, but this situation is not very frequent. There are not many studies that assess the efficiency of a change in administration route of the drug (105) or of opioid rotation (106).

The symptomatic treatment of constipation, delirium and itchiness are described in the relative sections of this CPG.

The SR (103) found little evidence about efficient measures to treat the different side effects of opioids. A great variety of drugs have been used in the symptomatic treatment of nausea and vomiting but there are no comparative studies among them.

SR of case series 3

The familiarity of the practitioner with the drugs, its profile of adverse effects and interactions with other drugs all determine their choice. In our setting, metoclopramide, haloperidol or corticosteroids can be reasonable options (103).

There are no RCTs that assess the treatment of opioid-induced myoclonus. The evidence derives from case series: baclofen, benzodiazepines (diazepam, clonazepam and midazolam) and valproic acid were used. Myoclonus is associated with high doses of morphine, so the reduction of the dosage is the first measure to be taken into account.

Rotation of opioids

If adequate analgesia is not obtained or if there are side effects that lead to the suspension of the drug, the strategy of replacing the initial drug with a second opioid is proposed. This strategy is still not assessed in clinical trials. There are two reviews of prospective and retrospective case series that showed an improvement with the change of opioid (106; 107). It can be an alternative for side effects. The second most commonly used opioid in both SRs is methadone; its main disadvantage is the unpredictable pharmacokinetics and variability in the response, which requires expert personnel for handling. Other alternatives that have not been assessed so much but which are easier to manage include fentanyl, oxycodone and hydromorphone. Fentanyl presents the added advantage of transcutaneous administration.

There is great individual variability in the response to opioids. The dosage conversion tables are provided as reference and their use requires meticulous evaluation, monitoring the individual response to the treatment.

Expert opinion 4

The criteria for the use of laxatives must be given at the onset of the treatment with opioids; at times anti-emetics may be indicated. If the symptom is difficult to control a change to fentanyl can be tested, as it has been associated with a lower incidence of constipation (108; 109).

Adjuvant analgesics

RCT 1+

Adjuvant analgesics are drugs whose main action is not analgesic, but which work as such in some types of pain. They are used in PC to boost the effect of the analgesics, normally of opioids, to decrease their dosage, or in complex pain cases (110). Their use is practically compulsory in neuropathic pain or in painful bone metastasis. They are also used to treat the comorbility of patients in PC; for example anti-depressants for depression or anxiety associated with pain.

This therapeutic option is comprised of a very heterogeneous group of drugs. The most commonly used are summed up in table 6, with their main indications.

Table 6. Coadjuvant analgesics for pain treatment

Drugs	Indications
Anti-depressants **Tricyclic: amitriptyline, imipramine** **Serotonin-noradrenaline reuptake inhibitors (SNRI): duloxetine, venlafaxine** **Selective serotonin reuptake inhibitors (SSRI): fluoxetine, paroxetine, sertraline, citalopram** **Others: trazodone**	• Neuropathic pain* (tricyclic, duloxetine) • Pain associated with depression or anxiety
Anti-convulsants **Carbamazepine, gabapentin, pregabalin**	• Neuropathic pain*
Local anaesthetics **Lidocaine, capsaicine**	• Neuropathic pain* • Muscular skeletal pain (capsaicine)
Antagonists of N-methyl-D aspartic **Ketamine**	• Reduction in opioid dosage • Refractory neuropathic pain
Corticosteroids **Dexamethasone, methylprednisolone, others**	• Asthenia, anorexia, spinal cord compression, SCS, bone metastasis, increase in intracranial pressure, bowel obstruction
Muscle relaxers **Cyclobenzaprine, metocarbamol, baclofen**	• Muscular skeletal pain • Muscular spasms
Benzodiazepines**	• Anxiety associated with pain**
Bisphosphonates **Pamidronate, zoledronic acid**	• Useful in case of bone metastasis***
Radioisotopes **Strontium-89, lexidronam, samarium-153**	• Useful in case of bone metastasis***

* See neuropathic pain section; ** See anxiety section; *** See metastatic bone pain section. SCS: spine compression syndrome.

Although the use of adjuvants is very widespread, there are not many clinical trials that have studied their efficiency in PC. In many cases their use is catalogued as adjuvants to commonly used drugs for treating multiple symptoms of the patients. This is one of the reasons that explain the variability in adjuvant drugs in literature on PC (110).

Treating the symptoms also improves the pain, although it is impossible to know for sure if this is due to an independent analgesic effect of the drug. For example, corticosteroids are widely used in PC due to their anti-inflammatory action, resulting in a relief of symptoms, including pain.

SR of RCT 1+

In the SR of the AHRQ of 2004 (89) 17 RCTs were located on the use of adjuvant drugs in cancer patients, including trazodone, amitriptyline, methylphenidate, phenytoin or ketamine; no RCT was found on corticosteroids. A later RCT (111) on the use of corticosteroids as an additional therapy to opioids showed the need for further research in this field.

Ketamine is a general anaesthetic that has a central analgesic effect as it produces a block of N-methyl aspartic receptors. A Cochrane SR studies the effect of ketamine (112) as adjuvant treatment to morphine. The SR selected two RCTs. In one of them, ketamine was administered by intrathecal route to 20 patients, at a

dose of 1 mg/kg; in the other RCT, IV route was used at a dose of 0.25-0.5 mg/kg in 10 patients. Ketamine proved to be efficient in both studies. The side effects are frequent: delirium, hallucinations, etc. These effects can be more frequent in patients in PC, so their use must be limited to selected cases and managed by expert personnel.

Trials that support the use of adjuvant drugs in PC mainly originate from studies performed in other different contexts (110; 113); even here, the evidence on the analgesic efficiency of drugs such as muscle relaxers is limited and contradictory (110).

Case series 3

Alternative and supplementary therapies

Acupuncture: One SR (114) and a report by the Andalusia Agency of Health Technology Assessment (115) addressed this topic. Both included two RCTs on ear acupuncture in the treatment of pain in cancer patients but no conclusive results could be drawn.

SR of RCT 1+

Music therapy: The Cochrane SR (116) that studies the analgesic effect of music in pain in general also included studies on patients with oncological pain. It found a statistically significant effect on pain relief and on the need for analgesia, but of uncertain clinical importance.

Aromatherapy and massage: The Cochrane SR (117) studied both interventions in cancer patients. They conclude that there is limited evidence about their efficiency on anxiety in patients in PC, not finding sufficient proof with respect to their effect on pain.

Other treatments: different reviews found little evidence about other treatments such as muscle relaxation or hypnosis (89; 118).

Another recent SR (199) assessed the effects of meditation and massage on patients in EOL. Although some RCTs point to positive effects on pain and other variables, such as anxiety, the biases in the selection of patients and in the designs of studies make it difficult to generalise these findings.

The assessment of all these therapies is an area for future research in the field of PC, too.

6.2.5. Neuropathic pain

No RCTs have been specifically on patients in PC with neuropathic pain, so the findings of studies performed on other populations (88), mainly in diabetic neuropathy and in postherpetic neuralgia need to be extrapolated.

SR of RCT 1+

There is consistent evidence about the efficiency of tricyclic anti-depressants. Amitriptyline has been studied the most (113; 120). Anti-epileptics (carbamazepine, gabapentin, pregabalin) (121;122) have also proven efficient. There is evidence about the efficiency of opioids (123;124). A specific SR on neuropathic pain in diabetes (125) showed moderate efficiency of opioids in these patients.

Capsain as an external analgesic, applied at concentrations of 0.075% 4 times a day, is moderately efficient in neuropathic pain, but it presents problems of local tolerance (125; 126). It can be used in association with other treatments or in the case of failure of the initial therapy.

Lidocaine for external use can be used, but its efficiency is more controversial (129), so it is an alternative in the case of failure of the previous options.

RCT 1+

One RCT (127) compared the combination of morphine with gabapentin with each one of the monocomponents in patients with diabetic neuropathy or postherpetic neuralgia. The pain relief was greater with the association; the most frequent adverse effects of the combination were constipation, sedation and dry mouth.

Tricyclic anti-depressants are the first option when neuropathic type pain is suspected in a patient in EOL. Anti-epileptics can be used in the case of intolerance. When the patient has associated pain that requires analgesia with opioids, these are the first option. The association of morphine with gabapentin can be contemplated.

6.2.6. Breakthrough pain

RCT 1+

The most commonly used drug is oral morphine, although this practice has not been assessed by RCT. Until not very long ago, morphine, used in our setting, was in tablet form, whilst in other countries it has been used in oral solution. This latter presentation is now available in Spain. The recommended dosage of morphine in breakthrough pain is 1/6 of the total daily dose of morphine.

SR of RCT 1+

A specific preparation of fentanyl has recently been developed for breakthrough pain (oral transmucosal fentanyl), which has been assessed in a SR (128). This publication includes the search studies for drug dosage and the only comparative RCT with respect to oral morphine. The SR does not perform a meta-analysis, but demonstrates the efficiency of oral transmucosal fentanyl. The study that compares it with oral morphine (129) shows quicker pain relief with fentanyl, but with the disadvantages of the difficulty in adjusting the dosage and its high cost.

6.2.7. Metastatic bone pain

Pain is the most common cause of the presentation of bone metastases. It is estimated that two thirds of the radiological metastases are associated with pain. Bone metastases are very common in prostate, breast and lung neoplasias. Apart from the pain relief, the aim of the treatment of bone metastases is to prevent complications, such as hypercalcaemia, fractures and neurological lesions (above all malignant spinal cord compression). The choice of the most suitable treatment requires assessment on all the above variables.

The available treatments for bone metastases, apart from analgesia (according to the analgesic ladder with emphasis on the use of NSAID), are bisphos-

phonates, radiation therapy, chemotherapy, radioisotopes and surgical techniques. There are no direct comparisons between the different options.

Chemotherapy depends on the original tumour. The commonly used criteria to deal with breast and prostate tumours alleviate the pain associated with bone metastases. It is not the aim of this CPG to go deeper into the types of chemotherapy or into surgical techniques.

Calcitonin has not proven to be efficient in metastatic pain (130).

SR of RCT 1+

The efficiency of bisphosphonates in patients with bone metastases has been the aim of two SRs (131; 132). There are also specific reviews on prostate cancer (133) and breast cancer (134).

The Wong SR (131) focused exclusively on pain relief. It included 3,582 patients, some RCTs on patients with breast cancer, prostate cancer and multiple myeloma and 10 RCTs on people with different types of cancer. The latter were in the most advanced state of the illness. The treatment achieved pain relief and a reduction of the consumption of analgesics.

SR of RCT 1+

The Ross review (132) included IV pamidronate, IV zoledronic acid, oral etidronate and oral clodronate in breast cancer, multiple myeloma, prostate cancer and mixed population. The bisphosphonates reduced the fractures, [OR 0.65 (IC 95%: 0.55 to 0.78)], the need for radiation therapy and hypercalcaemia; but not malignant spinal cord compression (MSCC) or the need for orthopaedic surgery. The IV bisphosphonates were more efficient than the oral ones in increasing the time to the first bone event. No differences were observed between pamidronate and zoledronic acid.

In the more recent specific review by Pavlakis on breast cancer, which is more recent and with more studies, bisphosphonates (pamidronate, zoledronic acid, ibandronate, clordonate) reduced the risk of any bone event (new metastases, pathological fractures, need for radiation therapy, appearance or progression of pain) by 17%. IV pamidronate (90 mg every 3-4 weeks) and zoledronic acid (4 mg every 3-4 weeks) were the most efficient. In a RCT that compared zoledronic acid and pamidronate (133), the results were more favourable for zoledronic acid in the analyses of subgroups carried out *a posteriori* on women with lithic lesions and on those who received hormonal treatment. However, the authors of the review (134) conclude that with these data it is impossible to affirm the superiority of zoledronic acid over pamidronate.

The SR on prostate cancer included 10 RCTs (1955 patients) with clodronate (seven RCT) pamidronate, etidronate and zoledronic acid. The response rate to the pain was 27.9% with bisphosphonates compared with the 21.1% of the control group, [OR 1.54 (IC 95%: 0.97 to 2.44)]; and the bone events decreased with the treatment, [OR 0.79 (IC 95%: 0.62 to 1.00)].

The treatment has to last for at least six months. This is decisive for the choice of patients. Oral bisphosphonates were associated with gastrointestinal side effects, whilst pamidronate and zoledronic acid produced more serious reactions.

SR of RCT 1+

Palliative radiation therapy has been the subject of several SRs (136; 137), updated through a recent publication (138). These reviews have studied both the efficiency of palliative radiation therapy and the therapeutic outline (simple

opposed to fractioned). The McQuay review showed a complete response rate to pain of 25% with radiation therapy, compared with the theoretic rate of 1% without treatment (137).

The Chow review (138) included seven new RCTs. The response rate, defined as the relief of at least 50% the pain, was similar with the single dose (58%) and with multiple doses (59%). The need for retreatment was greater with simple radiation therapy (20%) compared with fractioned radiation therapy (8%). No statistically significant differences were observed in the fracture rate (3.2% with simple radiation therapy compared with 2.8% fractioned radiation therapy) or in the malignant spine compression ones (2.8% compared with 1.9%). The side effects were not described in all the studies. In two studies there were more side effects in the fractioned therapy group. It is not possible to identify which subgroup of patients benefits more from fractioned therapy with the SR.

SR of RCT 1+

The use of radioisotopes has been assessed in the three SRs: the SR published in 1999 by McQuay (136) and the more recent ones by Roqué (139) and Finlay (140); the latter was carried out in the context of the preparation of a Canadian CPG.

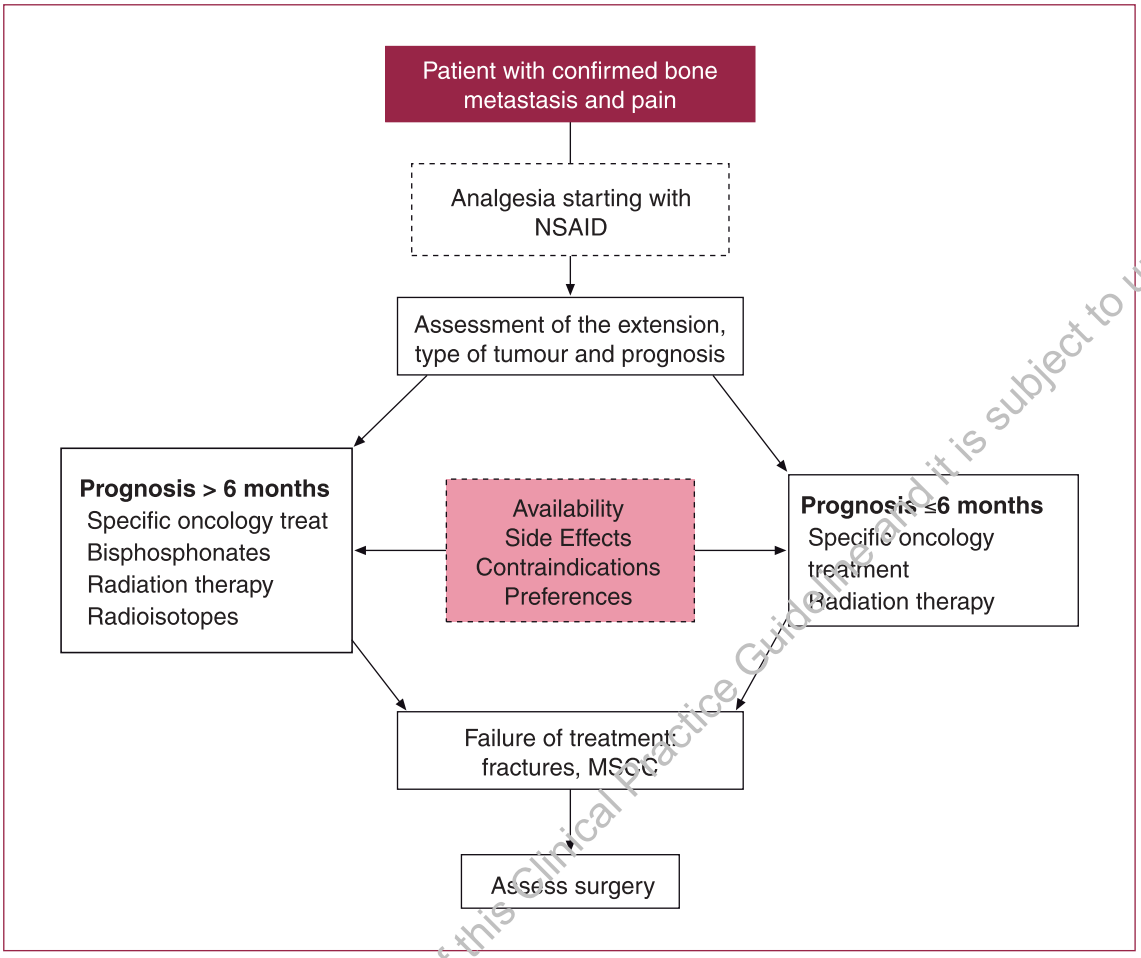
The Roqué review included four RCTs (325 patients), the majority with prostate cancer. Three of the RCTs used strontium-89 and one lexidronam. The treatment showed a tendency for the pain to improve with no modifications in new bone events (such as fractures or MSCC). The most frequent side effects were thrombocytopenia and above all leucopoenia [RR 4.56 (IC 95%: 1.22 to 17,08)].

The Canadian SR used broader selection criteria and also included RCT in phase II. The majority of the studies were performed on patients with prostate cancer resistant to the hormone treatment (80%-90%), breast and lung cancer with multiple bone metastases. The review did not perform meta-analysis. The strontium-89 and the samarium-153 proved to be moderately efficient.

Based on these findings, it can be concluded that further research is necessary before proposing the use of radioisotopes as a first line of treatment for bone metastases.

Figure 8 sums up the treatment of patients with painful bone metastases.

Figure 8. Treatment of patients with painful bone metastases



Summary of evidence

3	With the WHO analgesic ladder, adequate pain control is achieved in a percentage that varies between 45% and 100% of the cancer patients, although it has not been assessed with RCTs (95; 96).
1+	There is no evidence that supports or advises against the association of opioids with NSAID (92).
1+/3	Adjuvant drugs are efficient in pain treatment in patients in PC (89; 110).
1+	Oral transmucosal fentanyl is equally effective as oral morphine for breakthrough pain (128) (129).
1+	There is reduced and controversial evidence about the efficiency of alternative therapies in pain treatment in PC (89; 115-118).
1+	Tricyclic anti-depressants (amitriptyline) (113; 120), anti-epileptics (carbamazepine, gabapentin, pregabalin) (121; 122) and opioids (123-125) are efficient in relieving neuropathic pain.

1+	Methadone, oxycodone or fentanyl are not more efficient than oral morphine for treating pain in patients in PC (93; 94; 102).
1+	There is limited evidence that the combined treatment of drugs with different action mechanisms can improve the response to the treatment, also increasing the adverse effects (127).
1++	Calcitonin does not improve the pain or morbidity associated with bone metastases (130).
1++	Radiation therapy is efficient in pain relief and morbidity associated with brain metastases (136-138).
1++	A single dose of radiation therapy is similar to the fractioned dose in pain relief associated with bone metastases, risk of fractures and spinal cord compression, with a slight increase in the need for re-treatment (138).
1++	Bisphosphonates are efficient in pain relief and in the decrease of complications associated with bone metastases (131;134). These findings are more consistent for breast cancer (131) and to a lesser extent for prostate cancer (133).
1++	Pamidronate IV and zoledronic acid IV are more efficient than other bisphosphonates in the relief of morbidity associated with bone metastases (131; 133).
1+	Radioisotopes are moderately efficient in relieving pain associated with bone metastases (139).

Recommendations

D	When caring for pain in PC, an integral assessment of the pain should be made, bearing in mind its origin, aetiology, intensity and repercussion on the patient and family.
D	The team of professionals treating pain in PC should instruct and involve the patient and his/her family in the correct use of proposed analgesic measures.
C	When evaluating pain, validated scales can be used to quantify the pain. The use of visual analogue scales (VAS) or the Brief Pain Questionnaire (BPQ) is recommended.
D	The use of the WHO analgesic ladder together with adjuvant drugs, if necessary, is recommended in the pharmacological treatment of pain. The drugs must be used according to the intensity of the pain and the comorbidity of each patient.
D	Criteria must be provided for administering analgesics. The response to the treatment must be monitored, adapting the dose individually.
A	Oral morphine is the treatment of choice on the third step of the analgesic ladder.
B	Tricyclic antidepressants are the drugs of choice in neuropathic pain. In the event of intolerance or contraindication, anticonvulsants (gabapentin) are recommended. Opioids can be used in neuropathic pain and they are the first option to be considered in the case of pain associated with another aetiology that requires a level of analgesia with these drugs. When response to the treatment is insufficient, drugs with different action mechanisms can be associated, monitoring the response and the adverse effects.

B	Morphine is the drug of choice in breakthrough pain (1/6 of the total daily dosage per dose). The alternative treatment is oral transmucosal fentanyl.
B	Alternative therapies do not constitute first line treatment for pain in patients in PC.
D	Patients with painful bone metastasis should receive analgesia according to the WHO ladder, starting with NSAID.
B	Radiation therapy is the treatment of choice in painful bone metastasis.
B	The use of bisphosphonates (pamidronate and zoledronic acid), depending on the type of tumour and its extension, is recommended in patients with painful bone metastasis with a prognosis of over six months.
B	Radioisotopes should not be used as first line of treatment for bone metastases, although they could be useful in selected cases, such as patients with prostate cancer when hormonal treatment has failed, or breast or lung cancer where radiation therapy, chemotherapy and bisphosphonates are contraindicated.

6.3. Asthenia, anorexia-cachexia and dehydration

The questions that are going to be answered are:

- What is the most suitable treatment for asthenia in people in EOL?
- What is the most suitable treatment for anorexia-cachexia in people in EOL?
- What is the most suitable treatment for dehydration in people in EOL?

6.3.1. Asthenia and anorexia-cachexia

Asthenia is understood as the state that includes tiredness following minimal effort, reduction of the functional capacity, feeling of weakness defined as feeling incapable of starting any activity in advance, reduction of concentration capacity, alteration of memory and emotional lability (141).

Anorexia, defined as lack of appetite and weight loss that can accompany asthenia in these patients.

Cachexia is the manifestation of undernourishment and weight loss that can be associated with asthenia, above all in the patient's final phase in PC.

Up to 80% of cancer patients with advanced illness can present cachexia, due to the metabolic changes caused both by the substances secreted by the tumour and the immunological response to it (142).

Asthenia

Asthenia is the most frequent symptom in PC; it can occur in up to 90% of the cases (79). There are many factors involved and they can appear at different times in the same patient (see table 7).

Asthenia can have a very important individual subjective component. The team must bear in mind that each patient needs to adapt his or her activities to the new situation. Correct communication, support and advice by the team can reduce the burden represented for the patient and his or her carers by the reduction of functional capacity. **Expert opinion 4**

The second step is the evaluation and whenever possible the treatment of the causes of asthenia (table 7).

No treatable cause is identified in many cases. The therapies that can be used may be pharmacological and non-pharmacological (143).

Table 7. Factors related to asthenia in patients in palliative care.

- Pain
- Anaemia
- Infections
- Chemotherapy and radiation therapy
- Depression, insomnia and anxiety
- Paraneoplastic syndromes
- Cachexia
- Drugs
- Metabolic disorders
- Associated morbility: heart failure, COPD, etc.

In agreement with the results of a review that included 15 studies (five RCTs), physical exercise, above all aerobic exercise, improve asthenia (143). Home and outpatient programmes were included, but only a few studies were performed on patients with advanced cancer. Exercise requires a careful selection of patients and adequate infrastructures. **RCT 1+**

The psychosocial interventions have also proved to be useful in treating asthenia.

The evidence about the efficiency of the pharmacological therapy is limited and it is an area that requires further research. There is no systematic review on the drugs used in asthenia. Erythropoietin and darbepoetin have been used in patients with renal failure and in cancer patients with anaemia, above all when produced by chemotherapy. A Cochrane SR (144) assessed the efficiency in cancer patients, many of them receiving chemotherapy treatment. Erythropoietin and darbepoetin are efficient in reducing the needs for transfusion and improving the quality of life, but they do not affect survival and entail an increase of thromboembolic events. **RCT 1+**

Corticosteroids (prednisone 20-40 mg/day or equivalent dose) have been widely used, although very few RCTs have been performed (145).

Anorexia and cachexia

The assessment of anorexia requires working together with patients and their families, and good communication is an essential component. The team must bear in mind the cultural and social meaning of the lack of appetite and diet difficulties. In the Shargee SR (146), based only on articles published in the English language, the social and cultural meaning of loss of appetite and diet difficulties for patients and carers were studied. The latter consider them to be more important and relevant than the actual patients.

The evidence that assesses the interventions is included in several SRs carried out with different approaches (147-149).

SR of RCT 1++

A Cochrane SR showed that megestrol acetate (MA), at a dosage of 40-800 mg/day, is efficient to increase appetite and gain weight in patients with advanced illness and clinical diagnosis of anorexia and cachexia. The SR included 4,123 patients with cancer, HIV-AIDS and other chronic illnesses. The average duration of the studies was 12 weeks. The RR for the increase in weight was 2.79 (IC 95%: 1.56-5.00); for patients with cancer, RR 3.09 (IC 95%: 1.68-5.69) and a weight difference of 3.56 kg (IC 95%: 1.27-5.85). No effect on the quality of life was observed. The following side effects were observed: impotence, oedema in lower limbs, deep venous thrombosis and gastrointestinal intolerance, although a statistically significant difference was only reached in the case of the oedemas.

In the subanalysis that compared megestrol acetate with corticosteroids there were no differences between both measurements in the improvement of appetite or in the weight.

SR of RCT 1+

The Yavuzsen SR is based on 55 RCTs (148) on the efficiency of pharmacological treatment in anorexia, weight loss and asthenia. Its results are consistent with those of the Cochrane review with respect to the megestrol acetate.

The corticosteroids methylprednisolone (32-125 mg/day), prednisolone (10 mg/day) and dexamethasone (3-8 mg/day) are also efficient in the improvement of appetite and increase in weight.

RCT 1 +

Respect to other drugs, there is little evidence and with contradictory results for cyproheptadine, pentoxyphylline and melatonin, so no recommendations on their use can be given. Respect to hydrazine sulphate, the SR included five RCTs but it only proved to be efficient in one, so their use is not advised.

RCT 1+

Psycho-stimulants such as methylphenidate or modafinil require further assessment in this indication (145). In one RCT, both methylphenidate and placebo were associated with an improvement in asthenia, but no significant differences were observed between them after one week's treatment. The intervention was accompanied in both groups by daily telephone calls by nurses. The authors conclude that longer studies are required and that the effect of the nurses' telephone calls should be explored as therapeutic intervention (150).

Summary of evidence

1+	Adapted aerobic exercise improves asthenia in patients in PC (143).
1+	Corticosteroids are efficient in treating asthenia and anorexia in patients in PC (147-149).
1++	Megestrol acetate is more efficient than placebo and equally efficient as corticosteroids in the improvement of appetite and weight (147-149).
1+	Pharmacological treatments with pentoxyphylline, ciproheptadine or melatonin show contradictory results in the treatment of anorexia-cachexia (147-149).
1+	Hydrazine is not efficient in the treatment of anorexia-cachexia (147-149).

Recommendations

D	The initial assessment by the team of a patient with asthenia, anorexia-cachexia includes the identification, if possible, and treatment of the triggering causes; advice on daily activities, rest and sleep adapted to each situation and an exploration of the expectations and beliefs about the diet of patients and carers.
A	Pharmacological treatment can be tested in selected cases where anorexia is a prevailing symptom, bearing in mind the accompanying symptoms, pharmacological interactions and possible side effects of the medication.
A	If pharmacological treatment is required, corticosteroids, in the first place, and megestrol acetate, as a second option, are the drugs of choice. The use of hydrazine is not recommended. Further studies with methylphenidate are required.

6.3.2. Dehydration

The correct hydration of patients in PC is a basic support measure if we bear in mind the wear represented by the evolution of the illness and the treatments.

The need for fluid intake by parenteral route can be posed in very advanced phases of the illness and it may be a difficult decision to take (151).

The beliefs and expectations of the patients, carers and professionals on the benefits of fluid intake in this phase have a decisive influence on the decision. The possible benefits and risks must therefore be examined.

There are two SRs (152; 153) that have assessed the relationship between fluid intake and the symptoms of patients in PC. There is little evidence as there are no RCTs or sufficient prospective studies.

There is a recent narrative review (154) that examines the different types of hydration: intravenous, subcutaneous and rectal. Hypodermoclysis has also been assessed in an SR published in 1997 (155) and updated in 2004 (156).

The Viola review (152) studied the relationship between the patient's hydration and fluid intake in terminal phases in any context of healthcare, the majority in oncology. The review was based on six studies (532 patients) with moderate quality and variable life prognosis. The improvement in some of the symptoms commonly attributed to dehydration (such as thirst, dry mouth or confusion) with liquid intake could not be demonstrated in a consistent manner. One of the reasons is that these symptoms have a multifactor aetiology in PC and the patient's hydration is only one of them.

SR of observational studies 3

The confusion produced by opioids is related to situations with low fluid intake. The possibility of increasing lung secretions, congestive heart failure and the need for a urinary probe that may represent the overload of volume must be taken into account in this situation (154).

Expert opinions 4

The Burge review (153) explored the social-cultural and symbolic aspects of fluid intake and the role of the carer in hydration and in feeding. It coincides with the previous review as it maintains the same doubts about the relationship between symptoms and liquid intake.

SR of observational studies 3

To take decisions about parenteral hydration there is broad consensus about the need for good communication between the team and the sick person and his or her family, explaining the existing evidence about its advantages and disadvantages (154). It must be taken into account that this measure may, in some cases, mean admission into hospital.

As with the treatment of anorexia-cachexia, the beliefs about the meaning of hydration for the patient and his or her family must be explored.

Another question that may affect the decision about the use of the parenteral route is the choice of the most appropriate method. Endovenous administration of liquids or subcutaneous administration (hypodermoclysis) can be used in PC. Table 8 sums up the advantages and disadvantages of this method (154).

The evidence about the use of hypodermoclysis is included in two SRs (155; 156), which include RCTs performed with patients of advanced age, some in the context of PC. The efficiency of SC route is comparable with the intravenous route. Hypodermoclysis requires solutions with electrolytes and saline. Solutions without electrolytes cannot be used by this route (155). It can be administered continuously for 24 hours at a rate of 40-60 ml/hour, night (80 ml/hour) or via infusion in bolus of 500 ml/hour 2 or 3 times a day.

SR of RCT and case series 1+/3

Table 8. Advantages and disadvantages of hypodermoclysis

Advantages	Disadvantages
• Low cost. • Less need for supervision. • It can be maintained for 5 to 7 days. • Less painful insertion and easier to use than IV route. • Possibility of home use or in closed institutions without the need for hospital admission. • Absence of thrombophlebitis and less incidence of local effects. • Advantages in nervous patients, as the need for new venous approaches is avoided due to self-removal of the catheter.	• It is not valid for rapid administration. • The maximum volume to be administered is 3 litres(/day but it requires two simultaneous accesses (quite uncommon situation) • Oedema and local skin reactions (not very frequent) • Possible risk of haemorrhage in patients with coagulation disorders. • Lack of knowledge and expertise of health professionals regarding the technique.

There is a third alternative to endovenous and hypodermoclysis, the rectal route. It has only been described in case series and it permits the intermittent administration of liquids every 4 hours; it can be an alternative if it is impossible to use any other route (154).

Case series 3

Summary of evidence

3	There is little evidence that associates fluid intake with the relief of symptoms such as dry mouth, thirst and state of confusion (152; 153).
1+	Hypodermoclysis is a valid alternative to the administration of liquids by endovenous route (154).

Recommendations

D	The oral route is the route of choice for liquid intake; the use of parenteral route must be avoided when possible.
D	The administration of liquids by parenteral route requires an individualised evaluation, weighing up advantages and disadvantages. This evaluation must include the patients' and their family's expectations on the administration of fluids.
B	If parenteral rehydration is chosen, the subcutaneous route can be considered in the first place, so long as the necessary means and prepared staff are available.
D	If the SC and endovenous routes are not possible the use of the rectal route can be considered.
√	If parenteral rehydration is chosen outside the hospital, hypodermoclysis is the first option that must be considered.

6.4. Breathing symptoms

The questions that are going to be answered are:

- How efficient are opioids and adjuvant treatments in the treatment of dyspnoea?
- How efficient is oxygen in the treatment of dyspnoea?
- What is the most suitable treatment for coughing in people in EOL?
- What is the most suitable treatment for the obstruction of the superior vena cava?

6.4.1. Dyspnoea

According to the American Thoracic Society, *dyspnoea* is defined as a subjective experience of breathing distress that consists of qualitatively distinct sensations that vary in intensity. For patients, dyspnoea is just as difficult to put up with as pain (157). Its prevalence in PC is high; it can reach 85% in patients with CCI and more than 90% among patients with COPD (79).

The reversible causes of dyspnoea that have specific treatment must be treated. These are heart failure, the exacerbation of COPD and asthma, bronchospasm, cardiac arrhythmias, anaemia, pleural or pericardial effusion, or the superior vena cava syndrome (158).

On many occasions, the use of bronchodilators improves the patient's dyspnoea with reversible obstruction of the air tract (159).

Radiation therapy and chemotherapy can be useful in dyspnoea produced by metastatic or primary pulmonary neoplasm. The assessment of these two measures in this situation is not the subject of this CPG.

Evaluation of dyspnoea

In patients in PC it is generally advisable to evaluate the intensity of the symptoms narrated by the patient. A visual analogue scale can be used to evaluate the intensity of the dyspnoea or the effectiveness of the treatments. The correlation between hypoxia and dyspnoea is low and the correction of dyspnoea is more complex that that of hypoxia. In general, the routine use of trials (chest X-ray, gases, pulseoximetry, etc.) is not recommended (157).

Expert opinion 4

One systematic review evaluated the validity and reliability of the existing scales to assess dyspnoea in PC, mainly in the research context (160). Numeric Rating Scale (NRS), the modified Bord scale, The Chronic Respiratory Questionnaire Dyspnoea Subscale (CRQ-D) and Cancer Dyspnoea Scale (CDS) seem to be the most adequate but further research is required. The visual analogue scales have also been assessed, although they require a larger sample size to evaluate them.

SR of observational studies 2+/3

General measures

The general measures are: keeping the room cool, using fans, avoiding irritants – such as smoke– or few people remaining in the room. In the case of an acute attack of dyspnoea it is important to accompany the patient (157).

Oxygen

SR of RCT 1+

One SR evaluated the usefulness of oxygen to alleviate non-exertional dyspnoea in patients with advanced illness of any cause (161), and included five studies with a total of 83 patients. Most of the patients had hypoxia; studies in ovarian and lung cancer and in COPD were included. The review concludes that the evidence about oxygen being able to improve non-exertional dyspnoea in selected patients is weak, but it is not known which patients can benefit from it. One single study (N = 38) included patients with hypoxia and both the oxygen and the air were efficient, so there is no conclusive evidence that supports the use of oxygen in patients without hypoxia. The inclusion of patients with COPD can also affect the results. Another test that included 33 patients with cancer and without hypoxia did not show any differences either between oxygen and air in the reduction of exertional dyspnoea (test when walking for six minutes).

SR of different types of studies 1+/2+

Another review (162) performed by a group of experts in palliative medicine analysed the studies on the efficiency of oxygen to treat dyspnoea in patients with COPD, advanced cancer or heart failure.

- Patients with COPD (the majority are small trials with crossed design): oxygen shows contradictory results in non-exertional dyspnoea and improvement of exertional dyspnoea compared with air. The response among different patients is very variable.
- Patients with cancer (the majority are small trials with crossed design): some patients with advanced cancer can benefit from oxygen, but there is no evidence that enables us to predict which patients are going to benefit.
- Patients with heart failure. There is not enough evidence to offer recommendations.

Opioids

SR of RCT 1+

A meta-analysis on the efficiency of opioid drugs in dyspnoea in advanced illnesses (163) found that these drugs are effective by oral and parenteral route, with an improvement of about 8 mm (on a visual analogue scale of 100). There is insufficient evidence about its usefulness by spray. The review included 18 studies, most of them crossed; the results in the subgroup of patients with COPD did not differ from the rest. The opioids studied were morphine, dihydrocodeine and diamorphine. The adverse effects described were normal (drowsiness, nausea, vomiting, dizziness and constipation). There is no evidence of them producing harmful effects on arterial gases or on oxygen saturation. A subsequent trial (16) confirmed the benefits of morphine in the treatment of dyspnoea in COPD, cancer and other respiratory diseases.

Adjuvant drugs: phenothiazines, benzodiazepines and systemic corticosteroids

SR of RCT 1+

A recent report (165) found a total of seven controlled trials (six randomised and one non-randomised) for these drugs in cancer patients. It found evidence of effectiveness for promethazine, and contradictory evidence for other phenothiazines in two small trials. The review concludes that promethazine can be used as a second line drug when opioids cannot be used, or in addition to these.

It found four trials with benzodiazepines (alprazolam, diazepam, clorazepate and midazolam). In general, no relief of the dyspnoea was observed with these drugs. One RCT compared the efficiency of morphine, midazolam and the association of both in 101 patients with illnesses in very advanced stages (166). A greater proportion of patients presented an improvement of the dyspnoea in the group of combined therapy with respect to the monotherapies. There were no differences in the intensity of the dyspnoea.

Dyspnoea can co-exist with symptoms such as anxiety or panic in these patients.

Table 9. Drugs for dyspnoea in terminal patients (adapted from Gallagher) (157)

First line drugs	Adjuvant drugs
Patients in treatment with opioids: increase the dosage by 25%-50%.	Promethazine: 25 mg/8-12 h or on demand. Chlorpromazine: 7.5-25 mg PO or SC every 6-8 h, or on demand. Benzodiazepines (if associated panic or anxiety): clorazepam 0.5-1 mg every 4-12 h, or on demand or another BDZ.
Patients who do not take opioids: Morphine: 2.5-5 mg PO every 4 h. Oxycodone: 2.5-5 mg PO every 4 h.	

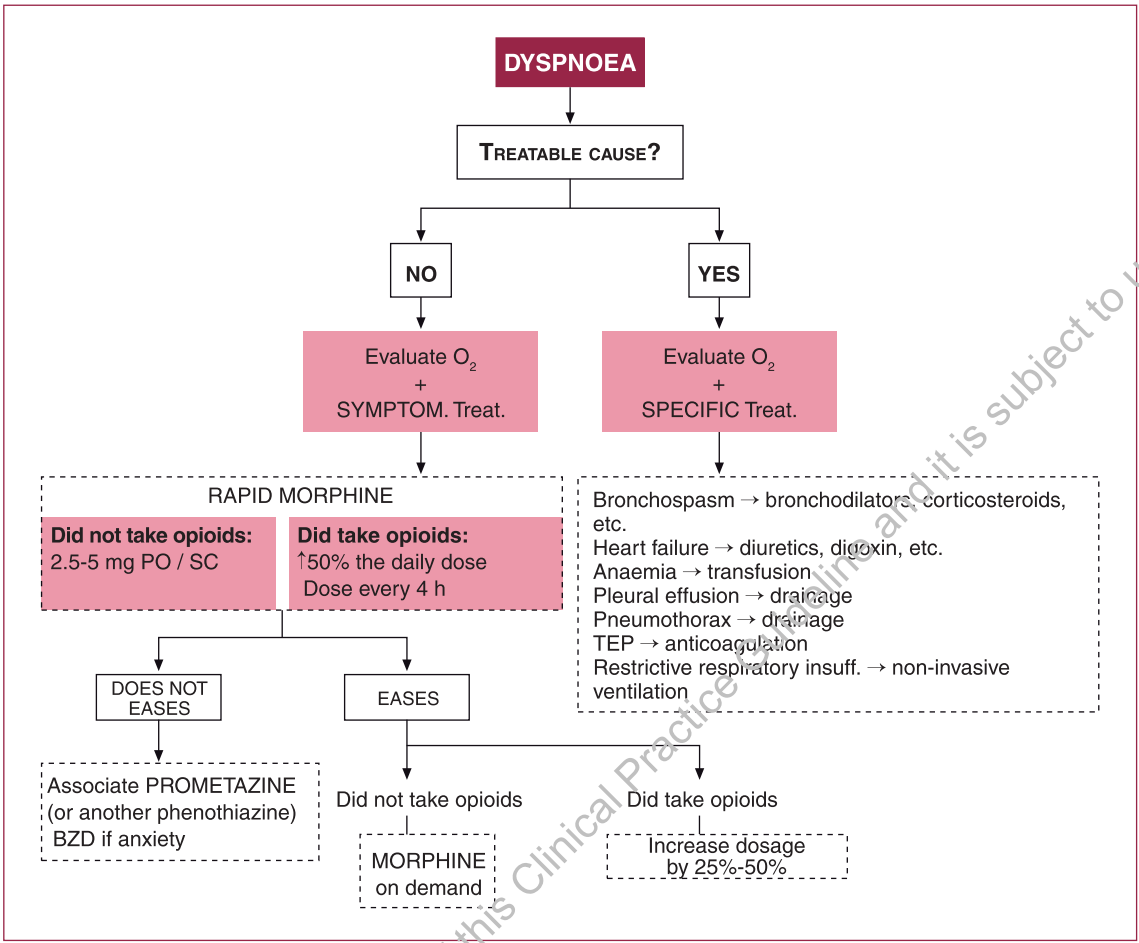
No studies with systemic corticosteroids were found.

Case series 3

However, corticosteroids are useful in dyspnoea in certain situations: COPD, asthma, cancer patients with tumour-caused airway obstructive problems or in carcinomatous lymphangitis (158). The drugs used to treat dyspnoea are presented in table 9.

The treatment of dyspnoea in patients in PC is summed up in figure 9.

Figure 9. Algorithm of treatment of dyspnoea in patients in PC



Non-invasive ventilation in patients with motor neurological diseases

Observational studies and case series 2+/3

One CPG (167) has reviewed the evidence about non-invasive ventilation in patients with motor neurological diseases treated at home via positive pressure devices. There is evidence from observational studies and case series that non-invasive ventilation can alleviate the symptoms, prolong survival and improve the quality of life in patients with motor neurological diseases in advanced status (the majority of the studies include patients with limited pulmonary capacity and a short life prognosis). However, not all patients tolerate or want this. The decision to use non-invasive ventilation is very complicated and must be discussed with patients and their families. It must be carried out by professionals with adequate training.

Management of severe dyspnoea during the last hours of life

It is important for the doctor to be present. It is advisable to administer opioids by parenteral route (IV, SC or continuous infusion); phenothiazines can also be administered. They may require sedation (157). The association of midazolam with morphine may be useful (166).

Summary of evidence

2+	There are different scales to assess dyspnoea in PC, used mainly in the research context; more studies are required to select the most adequate (160).
1+	There is evidence that oxygen can improve dyspnoea in selected patients with cancer and COPD, but which patients can benefit the most is unknown. The majority of the studies include patients with hypoxia (161; 162).
1+	Opioids by oral or parenteral route are efficient drugs in the treatment of dyspnoea in advanced illnesses. There is insufficient evidence by spray (163; 164).
1+	romethazine is efficient to alleviate dyspnoea in patients with cancer. The evidence for other phenothiazines is contradictory or non-existent. Benzodiazepines are not efficient, except in the very advanced phase of the disease (midazolam) as additional therapy to morphine (166). No RCTs were found for systemic corticosteroids (165).
2+/3	Non-invasive ventilation can alleviate the symptoms, prolong survival and improve the quality of life in patients with motor neurological diseases in advanced stages. However, not all patients tolerate or want it.
3	Corticosteroids produce relief in dyspnoea in patients with tumour obstruction of the airway or carcinomatous lymphangitis, COPD and asthma (158).

Recommendations

D	The reversible causes of dyspnoea must be treated specifically, such as heart failure, exacerbations of COPD, cardiac arrhythmias, anaemia, pleural or pericardial haemorrhage, bronchial infection, pulmonary embolism or superior vena cava syndrome.
D	The intensity of the symptoms related by the patient should be evaluated.
B	If there is a lack of suitable evidence to be able to predict which patients can benefit the most from treatment with oxygen to alleviate the dyspnoea, it is advisable to evaluate the continuity of the treatment according to individual response.
A	Opioids by oral or parenteral route are first choice drugs for treating dyspnoea.
B	Promethazine can be used as a second line drug when opioids cannot be used or in addition to these. The use of benzodiazepines is not recommended for dyspnoea, except for situations of anxiety or panic, or in very advanced phases of life as an additional therapy to morphine (midazolam).
D	Corticosteroids are indicated in the case of dyspnoea produced by asthma, COPD, tumour obstruction of the airways or carcinomatous lymphangitis.

6.4.2. Coughing

Coughing is present in 4%-86% of patients with lung cancer and in 23%-37% in other cancers. It can occur in 59% of the cases in patients with chronic pulmonary diseases (158).

As with the general population, coughing in PC can be productive or non-productive. The treatment affects the latter, as productive coughing favours the elimination of bronchial secretions (168).

Coughing in cancer patients may be due to different causes, which may or may not be related to their main illness (see table 10).

Table 10. Causes of coughing in patients with advanced cancer (modified from 169; 170)

Related to the tumour	Not directly related to the tumour
• Tumour mass • Pleural effusion • Pericardial effusion • Atelectasis • Obstruction of the superior vena cava • Infections • Fistulas in the oesophagus or in the respiratory tracts • Carcinomatous lymphangitis • Complications of radiation therapy and chemotherapy	• Postnasal dripping • ACE and other drugs • Asthma • COPD • Bronchiectasis • Pulmonary thromboembolism • Heart failure • Gastro-oesophageal reflux • Tympanum irritation

The first measure to address coughing in PC is to threat its causes, whenever possible.

In the cases of primary cough produced by lung cancer, the specific treatment with chemotherapy and above all with radiation therapy (171) is a measure of proven efficiency (172).

In some cases of lung neoplasia that differs from small cell neoplasia, the brachytherapy can be an option to be considered if coughing persists despite palliative radiation therapy (173).

Pharmacological treatment is necessary on many occasions. There are multiple case series that describe the response rate to the treatment with different cough suppressants, most of the patients having lung cancer (74; 172). Very few RCTs have been performed as occurs in many other areas of PC.

Cough suppressants can be classified, according to their action, in central (opioids and non-opioids) or peripheral (direct or indirect action) (169) (see table 11).

Table 11. Classification of cough suppressants according to group and action mechanism

Central	Peripheral
Opioids	**Direct**
• Pholcodine* • Dextrometorphane • Codeine • Dihydrocodeine • Morphine • Hydrocodone*	• Levodropropizine • Benzonatate*
Non-opioids	**Indirect**
• Clobutinol* • Cloperastine	• Sodium cromoglicate • Antihistamines • Bronchodilators

* Not commercialised in Spain.

Not all opioids have been assessed in the treatment of coughing in PC; This is the case of fentanyl, hydromorphone and oxycodone.

The choice of drug and the administration routes depend on the individual situation of the patient, on the side effects or interactions and on the experience of use in PC. If an opioid is required dihydrocodeine can be chosen (174). Morphine is the drug of choice in presence of pain or dyspnoea associated with coughing. **Case series 3**

Levodropropizine can be used as an alternative, which is equally efficient as dihydrocodeine but produces less drowsiness (175). **RCT 1+**

Sodium cromoglicate has proven efficient in coughing in patients with lung cancer resistant to traditional treatment (176). **RCT 1+**

In case of coughs that are resistant to different cough suppressants, some authors recommend the use of sprayed anaesthetics such as bupivacaine or lidocaine (168). **Expert opinion 4**

If treatment for coughing due to COPD is required, codeine, dihydrocodeine or dextrometorphane can be used (177). **Expert opinion 4**

Summary of evidence

1+	Dihydrocodeine and levodropropizine have proven to be equally efficient in relieving coughing in cancer patients in PC. Levodropropizine produces less drowsiness (175).
3	Opioid central cough suppressants (pholcodine, codeine, morphine, hydrocodone) and non-opioid cough suppressants (clobutinol and cloperastine) improve coughing in cancer patients in PC (172; 174) (170).
1+	Disodium cromoglicate is efficient in coughing of patients with lung cancer when traditional treatment has failed (176).

Recommendations

D	Patients in PC with a cough require an individualised assessment to diagnose and, where possible, treat the specific causes of the cough. Palliative chemotherapy should be evaluated in cases of lung cancer.
D	To choose the drugs, it is recommended to evaluate other accompanying symptoms (pain, dyspnoea), the prior use of opioids, possible pharmacological interactions and administration route.
B	Dihydrocodeine, codeine, levodropropizine or cloperastine can be used as initial drugs.
C	Disodium cromoglicate can be used in patients with lung cancer whose cough does not respond to normal treatment.
D	If treatment is required for the cough, due to the COPD, codeine, dehydrocodeine or dextrometorphane can be used.

6.4.3. Obstruction of the superior vena cava

The *superior vena cava obstruction syndrome* (SVCO) arises due to a commitment of space at inter-pleural space level due to primary or metastatic tumour invasion. Normally, the obstruction is due to mediastinic adenopathies or to a bronchial origin tumour (main right and upper lobule), as lung cancer is the most frequent cause of SVCO.

Between 2 and 4% of patients with bronchogenic carcinoma will present an SVCO throughout their evolution. This risk increases to 20% in small cell carcinoma, due to its bronchial central origin (178).

The SVCO may also appear between 2% and 4% of the lymphomas that constitute the second cause.

The obstruction of the vein can be extrinsic, intraluminal, by fibrosis or thrombosis (158). The treatment depends on the rate of the obstruction and reflects the effect of the increase of the venous pressure. It normally starts with face oedema, cough, orthopnoea, cephalea and dizziness. In more advanced situations a florid manifestation of serious oedema appears on face and right arm, cyanosis, venous engorgement in vessels of neck and even brain oedema.

Case series 3

The treatments used until now have been radiation therapy (above all for non-small cell carcinoma), chemotherapy (small cell carcinoma), corticosteroids and the placement of stents. The latter present the theoretic advantage of speed in the relief of symptoms (178).

SR of RCT +1 Expert opinion 4

A Cochrane review (179) assessed the evidence on treatments in patients with lung cancer and SCVO. The review did not find any studies about the use of corticosteroids, although there is ample consensus about their use in this situation (dexamethasone at a daily dosage of 16 mg) (158).

In two RCTs, chemotherapy was compared with radiation therapy and individual treatments were evaluated (chemotherapy, radiation therapy and stents) in 44 observational studies.

Table 12 shows the percentage of improvement based on the Cochrane SR (179) and on another recent publication on stents (180).

SR of observational studies
3

Table 12. Average percentage of response to the palliative treatment in observational studies

Treatment		Improvement %	Relapse %
Radiation therapy or chemotherapy	Small cell carcinoma	77	17
	Other lung cancers	60	19
Stent (any type of tumour, including lung tumours)		80-95	13

The placement of stents is accompanied by an average mortality of 3.3%.

There is an unsolved debate about whether the placement of stents must be an initial treatment in SVCO. Comparative studies between radiation therapy and stents are necessary with an appropriate selection of patients. These studies are complicated to perform (181), so the individual situation of the patient and the technical availability in the local setting are decisive to decide upon the treatment.

Summary of evidence

3	Chemotherapy, radiation therapy, the combination of both and the placement of stents improve the SVCO in observational studies. There are no comparative studies between the different alternatives (179; 180).
3	The placement of stents achieves quicker relief of SVCO (179; 180).
4	There is consensus about the indication of corticosteroids in SVCO (158).

Recommendations

D	Patients with SVCO can be treated with corticosteroids, radiation therapy, chemotherapy or stent implantation, depending on their general state, histological type of the tumour and its extension, as well as the availability of techniques.

6.5. Psychological and psychiatric symptoms

The questions that are going to be answered are:

- What is the most suitable treatment for delirium in people in EOL?
- What is the most suitable treatment for insomnia in people in EOL?
- What is the most suitable treatment for anxiety in people in EOL?
- What is the most suitable treatment for depression in people in EOL?

6.5.1. Delirium

Delirium is defined as an acute confusional state resulting from diffuse brain dysfunction. It is clinically characterised by the simultaneous alteration of attention, perception, thinking, memory, psychomotor behaviour, emotion and sleep-wake cycle (182). Table 13 presents the DMS-IV diagnosis criteria for delirium (183).

Delirium is a frequent problem in patients in EOL; it is suffered by 28% to 83% of these patients; it varies depending on the population studied and the diagnosis criteria used and it is more frequent in patients with cancer (79). It can be present in up to 90% of patients in the last days of life (184) and its appearance is associated with a worse prognosis (34).

Table 13. DSM-IV criteria for the diagnosis of delirium

A) Alteration of consciousness with reduction of the capacity to focus, maintain or direct attention.
B) Change in cognitive functions (memory, orientation, language) or perceptive alteration that is not explained by the existence of prior or developing dementia.
C) Presentation in a period of time (hours or days) and tendency to fluctuate throughout the day.

Delirium must be suspected whenever there is an acute change in behaviour, the cognitive state or the state of alert of the patient, above all when there is dementia, recent surgery, auditory or visual handicap, consumption of alcohol, possibility of alteration of sodium, use of certain drugs, etc.

Expert opinion 4

The intensity of the manifestations is very variable, so some light forms that appear as unease or difficulty to reconcile sleep, for example, may go unnoticed, as the symptoms are attributed to other circumstances of the patient. At the other end, we find serious cases with intense unease that constitute a medical emergency (185).

Hypoactive delirium presents diagnosis problems, as it can be confused with depression. The evaluation of the cognitive state may help make the differential diagnosis between delirium and depression, as cognitive impairment is less frequent in depression (185).

There are instruments that may help with the diagnosis. Confusion Assessment Method (CAM), especially in its abridged version of four criteria, is a validated and simple instrument for detecting delirium (see table 14). It assesses the acute onset, the fluctuating course, the inattention and disorganised thinking or altered level of consciousness (186; 187).

The CAM-ICU (188) is recommended In intensive care units or in patients who are unable to communicate verbally.

It is important to identify the factors that cause or precipitate delirium, as they determine the need to use additional tests and the correct treatment. Often the aetiology is multi-factoral. Drugs are the most frequent isolated cause of delirium in PC (adverse effects at normal doses, intoxication or abstinence); this circumstance is especially important in patients undergoing treatment with opioids (186).

Monitoring the symptoms, an essential aspect of PC, may prevent the appearance of delirium, as the inadequate control of some symptoms, such as pain, may trigger the problem.

Table 14. Confusion Assessment Method

Point 1. Acute onset and fluctuating course

This feature is usually obtained from an observer (family member or nursing staff) and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Does the abnormal behaviour fluctuate during the day, that is, tend to come and go or increase and decrease in severity?

Point 2. Inattention

This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Point 3. Disorganised thinking

This feature is shown by a positive response to the following question: Was the patient's thinking disorganised or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Point 4. Altered level of consciousness

This feature is shown by any answer other than «alert» to the following question: Overall, how would you rate this patient's level of consciousness: alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (difficult to arouse) or coma (unable to be aroused)?

The main causes of delirium in PC in advanced cancer are summed up in table 15.

Table 15. Causes of delirium in advanced cancer

Causal category		Cause
Central nervous system illnesses		Primary and metastatic neoplasia of the brain; leptomeningeal metastatic disease; postictus.
Treatments	*Oncological*	Chemotherapy, radiation therapy.
	Psychoactive drugs	Opioids, benzodiazepines, tricyclic antidepressants, anticholinergic (oxybutynin, tolterodin), SSRI, neuroleptics, antihistamines, orthopramides, anticonvulsants (primidone, phenobarbital, phenytoin), anti-Parkinsonians.
	Others	Corticosteroids, antihistamines, anti-H2, ciprofloxacin.
Systemic disease	*Insufficiency*	Cardiac, respiratory, hepatic, renal.
	Infection	Any location, but especially pulmonary and urinary.
	Haematological	Anaemia, disseminated intravascular coagulation.
	Metabolic	Dehydration, hypercalcaemia, hyponatraemia, hypomagnesaemia, hypoglucaemia.
Psychosocial		Alteration of sight or hearing, pain, strange environment.
Evacuation		Urinary or faecal retention.

It is estimated that metabolic causes can be found in up to 18% of the cases. The team, depending on the patient's situation and his or her family, can determine the need to request tests (haemograph, glucose, creatinine, ions, calcium, phosphorus, magnesium and urine tests) or other trials such as CAT and ECG (188).

The treatment of delirium includes the simultaneous application of aetiological measures, general measures and symptomatic treatment.

The basis of its treatment is the correction, if possible, of the precipitating causes indicated above (table 15).

The evaluation of the use of certain drugs that may precipitate or worsen the delirium is especially important. If it is not possible to withdraw them, the reduction of the dosage or rotation of opioids can be evaluated if they are the cause of the manifestation.

The joint work with the family environment and patient's carers must provide adequate behavioural patterns and information and favour an environment that will contribute to the improvement of the manifestations and reduce their impact.

If the symptoms do not revert, pharmacological treatment is indicated.

Investigating the pharmacological treatment poses ethical problems in these patients, as the RCTs compared with placebo are not acceptable (184). This may be one of the reasons for the lack of randomised studies on the assessment of any treatment for delirium in PC. Most of the recommendations of this chapter are extrapolated from assessments of delirium outside the PC context. **SR of RCT 1+**

However, neuroleptics (above all haloperidol), benzodiazepines (midazolam or other such as lorazepam, clonazepam or diazepam) (189) or artificial hydration have been widely used in these patients. It must be taken into account that the benzodiazepines may, in turn, trigger delirium (table 15). **Case Series 3**

There is a specific Cochrane SR on delirium in PC (190), but it is based on one single RCT in patients with HIV-AIDS. Haloperidol by oral or IM routes has proven efficient with good tolerance. **SR of RCT 1+**

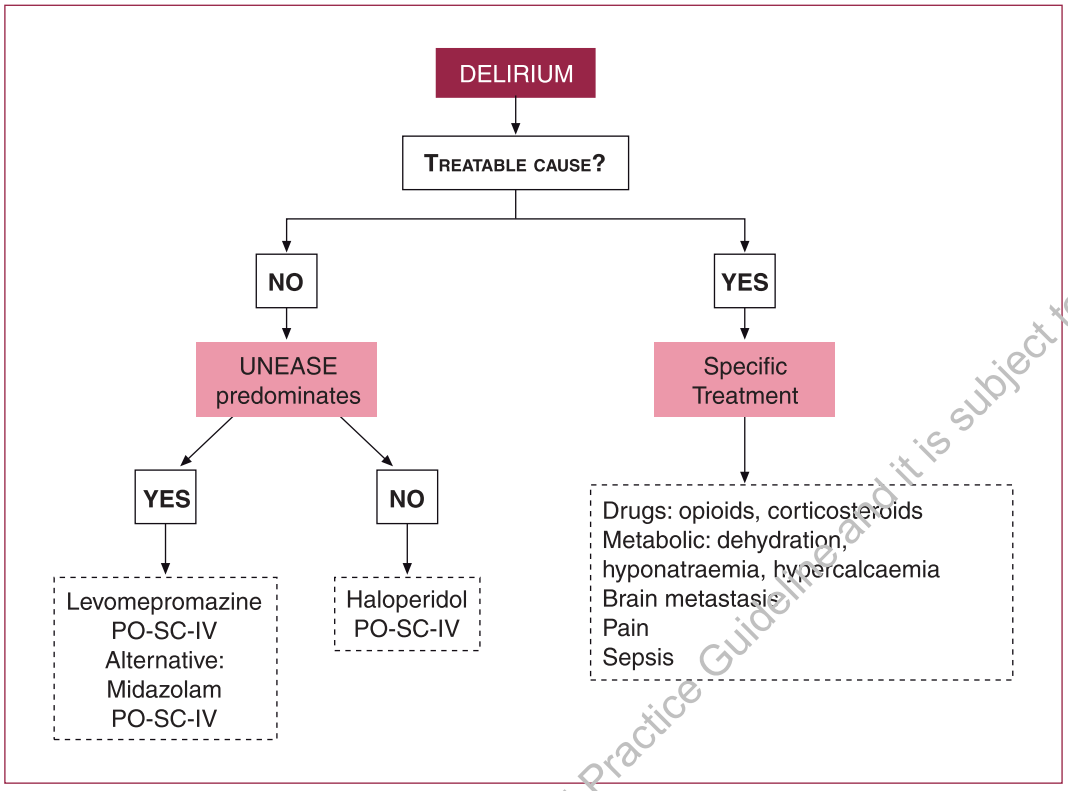
Hypodermoclysis can be useful if dehydration precipitates the delirium caused by the opioids (151). Apart from this indication there is little evidence about its efficiency in the treatment of delirium in general (184). **Case Series 3**

Some authors propose the association of lorazepam with haloperidol in the cases of delirium with anxiety or unrest, which could contribute to a reduction of the risk of extrapyramidal effects of the haloperidol (191). **Expert opinion 4**

In the cases of delirium with intense unease the use of levomepromazine and, alternatively, midazolam (191) is recommended. Clinical evaluation is necessary as well as close attention to the repercussions of the unease on the patients and their family to avoid premature sedation (185).

The treatment of delirium in patients in PC is summed up in figure 10.

Figure 10. Algorithm of treatment of delirium in patients in PC



Summary of evidence

1+	Haloperidol is efficient in controlling delirium in patients in EOL, with good tolerance (190).
4	Lorazepam can be useful as an additional therapy to haloperidol in the case of delirium with anxiety or unease. Levomepromazine can be used in delirium with intense unease (191).
1+/-	There is insufficient evidence about hypodermoclysis in delirium; it can be useful if it is a side effect of opioids (151).

Recommendations

D	The initial care of a patient with delirium should include the identification and treatment of the triggering causes, with special attention to the consumption of certain drugs (opioids); appropriate information to relations and carers and the evaluation of the need for pharmacological symptomatic treatment.
B	Haloperidol is the drug of choice to treat delirium.
D	Lorazepam can be added to haloperidol in the case of delirium with anxiety or unease.
D	Levomepromazine or, alternatively, midazolam can be used in delirium with non-controlled intense unease.

D	Hypodermoclysis can be used if delirium produced by opioids is suspected in dehydrated patients.
D	It is advisable to reserve the use of atypical antipsychotics for selected cases where haloperidol is contraindicated or is not tolerated. In situations such as dementias with Lewy bodies or in patients with Parkinson, where the use of haloperidol or risperidone is not recommended, other antipsychotics, such as olanzapine, clozapine or quetiapine can be resorted to.

6.5.2. Insomnia

Insomnia is a heterogeneous disorder that includes the difficulty in initiating sleep *(initial insomnia),* maintaining sleep *(intermediate insomnia)* awaking too early *(late insomnia)* and non-restorative sleep. The diagnostic criteria for insomnia (192) are set out in table 16. The repercussion of the patient's insomnia on family members and carers is important.

Table 16. Diagnostic criteria for insomnia

A) Difficulty sleeping characterised by any of the following criteria a) Difficulty initiating sleep (30 minutes or more). b) Difficulty maintaining sleep (more than 30 minutes of nocturnal awakenings) with corresponding sleep efficiency (ratio of total sleep time to time spent in bed) less than 85%.
B) Sleep disturbance occurs at least three nights per week.
C) Sleep disturbance causes significant impairment of daytime functioning (asthenia) or marked distress.

Sleep is altered in 50% or more of patients suffering from advanced cancer (193) and can reach 70%, depending on the baseline disease and care area (79).

Insomnia can appear as a reflection of the complex psychological reactions that take place in people who are in the EOL, due to a deficient control of the symptoms, and as a result of treatments. The factors involved in the appearance of insomnia in PC are summed up in table 17.

Table 17. Factors involved in insomnia in PC (modified of 192)

Predisposing • Increase of level of excitation • Women • Age • Family background of insomnia • Personal background of insomnia • Concomitant psychiatric illness (anxiety, depression, etc.)
Triggering • Psychological impact of illness • Mutilating surgery (with aesthetic or functional affection) • Hospital admission • Radiation therapy • Bone marrow transplant • Chemotherapy (nausea and vomiting) • Use of drugs (such as corticosteroids) • Menopause symptoms (hot flushes) • Pain • Delirium • Other symptoms (reflux, dyspnoea, pruritus, etc.)
Maintaining • Badly adapted behaviour faced with insomnia – Too long stays in bed – Irregular sleep-wake hours – Naps – Activities in bed that interfere with sleep • Wrong beliefs and attitudes towards insomnia – Not very realistic expectations about the needs for sleep – Wrong evaluation of difficulties sleeping – Wrong attribution of daytime alterations – Wrong ideas about the causes of insomnia

The main problem with detecting insomnia lies in not asking patients and, when they complain, overlooking it due to therapeutic nihilism or ignorance of the professional.

When the patient mentions difficulties maintaining sleep the precipitating factors of the awakenings must be sought. Among the aetiological aspects, ask about 1) physical disorders that make sleep difficult; 2) drugs; 3) psychological factors: worries, anxiety, expectations about sleep and beliefs about how this can affect the following day; and 4) sleep habits (naps, staying in bed, etc.).

The treatment of insomnia is multifactoral, due to the numerous causes that contribute to its appearance. Firstly the aetiological factors must be corrected. However, they are often not found or cannot be corrected. In this case, it may be necessary to resort to sleep hygiene, to non-pharmacological treatments and to pharmacological treatment (2).

The recommendations for sleep hygiene for people who receive PC are (2):

- Maintain regular hours if possible, above all the awakening in the morning.
- Avoid unnecessary times spent in bed during the day.

- Have a nap only when necessary, avoiding last time in the afternoon if possible.
- Have a timetable with activities during the day.
- Minimise interruptions of sleep during the night: noises, medication, etc.
- Avoid staying awake during the night for long periods in situations of stress.
- Eliminate unpleasant stimulations, such as touch, hearing or smell..
- Identify problems or affairs that have worried them during the day before going to bed, trying to address them with an active solution approach.
- Avoid stimulating medications or other substances (caffeine, nicotine) above all during the hours prior to going to bed..
- Maintain adequate pain relief during the night, preferably with medium-long lifespan analgesics.
- Use adequate medication after assessing insomnia.

Although there are many trials about the efficiency of treatments (psychological and pharmacological) in the general population, research in patients in PC is limited, above all in the case of non-pharmacological measures. It is necessary to resort to non-experimental studies or to expert opinions and extrapolate the data from other populations to prepare recommendations on the treatment of insomnia.

Several cognitive-behavioural therapies consider the benchmark treatment of insomnia. Their efficiency, proven in several meta-analyses in general population (194;195) is comparable with the efficiency of hypnotics, above all the initiating time, quality of sleep and duration of awakenings; and moderate over the total sleep time and number of awakenings. The most efficient treatments are the control of stimulations, sleep restriction and multifactoral treatment (multiple strategies). Education in sleep hygiene has modest benefits. Other treatments of proven efficiency are relaxation –although at times this has a paradoxical effect- and cognitive treatment, although this has always been studied within the context of a multifactoral strategy.

Studies on the efficiency of these treatments have always excluded patients with other illnesses, so it is not known if their results can be generalised to the area of PC.

With respect to pharmacological treatment, benzodiazepines are the most commonly used drugs. A systematic review did not find any randomised trial with these drugs in PC (196).

They have proven short-term efficiency in the general population. The most frequent side effects are lack of stability with a risk of falls, somnolence, sedation, cognitive and psychomotor disturbances, especially with prolonged action drugs. Other risks are tolerance and dependence, greater with those of medium-short lifespan.

Some sedative antidepressants (amitriptyline, trazodone, mirtazapine) can also be used as hypnotics, especially in patients with depression symptoms, although the sedative and anticholinergic side effects also limit their use (see appendix 5).

In any case, the treatment must be individualised depending on the patient (life prognosis, risk of pharmacological accumulation or interaction, etc.). **Expert opinion 4**

Summary of evidence

1+	No RCTs have been found on insomnia in patients in PC (196).

Recommendations

D	A patient with insomnia should be appraised via a semi-structured interview aimed at assessing the factors related to insomnia: predisposing factors, sleep hygiene, symptom control, side-effects of medication and patient's expectations respect to sleep.
D	Attempt to correct the predisposing factors to insomnia or those trigger it, when possible.
D	An initial approach is recommended via a cognitive-behavioural strategy in all patients with insomnia.
D	The prescription of benzodiazepine or a benzodiazepine receiver agonist is recommended for patients who do not respond well to non-pharmacological treatment or who cannot wait for its application.
D	In cases of associated depression or lack of response to benzodiazepines, anti-depressants with sedative action can be used to treat insomnia.

6.5.3. Anxiety

Patients with advanced illness are forced to face up to several psychological aggressions in a short period of time: the bad news of the diagnosis of a serious illness; the possibility of death in the short term; the uncertainty about how this process will develop, the symptoms of the actual illness, such as pain, dyspnoea, insomnia, etc., the side effects of the treatments, such as alopecia, mutilations, etc. Approximately half the patients manage to cope with these situations without their psychological reactions reaching a stage where they satisfy criteria of mental illness. However, the other half develops symptoms that constitute a mental disorder (189).

Anxiety is a state of distress characterised by the presence of a series of somatic, behavioural, cognitive and emotional symptoms:

- Somatic symptoms: muscular strain, trembling, palpitations, lack of stability, abnormal perspiration, diarrhoea, polyuria, etc.
- Behavioural symptoms: irritability, anxiety, etc.
- Cognitive symptoms: negative thoughts, fear or concern for the future.

Anxiety can appear as a normal state when it is proportional in intensity and duration to the cause that generated it; it is even an adaptative state, which permits

being alert and responding adequately in difficult circumstances. Anxiety disorders are characterised by excessive intensity or duration, to the extent that they significantly alter the person's life.

The anxiety diagnostic criteria based on the DMM-IV are included in table 18 (183).

Anxiety is frequent in patients in EOL. 13 to 79% of the patients can present anxiety depending on the type of baseline illness and the moment of its evolution.

The following are risk factors for the development of an anxiety disorder during palliative treatment: having previously suffered an anxiety disorder, the presence of anxiety when cancer was diagnosed, intense pain, functional limitation, age (more risk in young people), poor social support network and worsening of the illness. In patients in EOL, anxiety is not usually due so much to fear of death as to the other factors already mentioned, such as non-controlled pain, isolation and dependence (197).

Table 18. DSM-IV criteria for diagnosing the anxiety disorder

A) Excessive anxiety and worry (apprehensive expectation).

B) The person finds it difficult to control this state of constant worry.

C) The anxiety and worry are associated with three (or more) of the following six symptoms (some of which have persisted for more than six months)..

Note: In children only one of these symptoms is required:

1. feeling wound-up, tense or restless
2. easily becoming fatigued or worn-out
3. concentration problems
4 irritability
5. significant tension in muscles
6. difficulty with sleep (difficulty initiating or maintaining sleep or feeling or non-restorative sleep on awakening)

D) Anxiety, worry or physical symptoms provoke clinically significant distress or social and occupational impairment, or impairment of other important areas of the person's activity.

E) These problems do not appear during the course of a mood disorder, a psychotic disorder or a generalised development disorder.

The treatment of anxiety in patients in EOL depends on the cause, how it occurs and the context in which the consultation takes place (189).

A Cochrane SR (198) on this topic did not identify any RCTs carried out in PC so the recommendations are based on consensus and the extrapolation of tests on the general population. **SR of RCT 1+**

When the anxiety symptoms are slight, proportional and they appear in response to an identifiable factor, psychological support and the monitoring of the adaptative response are usually sufficient (197).

Although there is scientific evidence in favour and against their efficiency, basic non-pharmacological interventions to treat anxiety in patients in the end-of-life phase include support psychotherapy and cognitive-behavioural psycho- **SR of RCT 1+**

therapy. They must address patients and their families (199-201). There is no evidence about the efficiency of massage and meditation (119), hypnotherapy (199) or aromatherapy (117) either.

Expert opinion 4

The pharmacological treatment of anxiety of patients in end-of-life phase includes the rational and individualised use of benzodiazepines (BZD), neuroleptics, antidepressants, antihistamines and opioids (189).

Although there are no specific RCTs in PC, BZDs are the basis of the pharmacological treatment. Short-action BZDs (such as alprazolam and midazolam) or intermediate-action (such as lorazepam or lormetazepam) are the safest, as they avoid the accumulation of their metabolites in the weakened organism. Their greatest disadvantage is the possibility of anxiety appearing between doses or at the end of it, in which case the administration of a longer-action BZD is indicated, such as diazepam, dipotassium clorazepate or clonazepam. They are normally administered by oral route, but in a dying patient the administration of diazepam by rectal route or midazolam by subcutaneous route may be useful (202).

Typical neuroleptics—haloperidol, chlorpromazine— or atypical –- olanzapine, risperidone, quetiapine— can be useful when the anxiety is not controlled with BZD, or when accompanied by hallucinations or delirium; furthermore, they are safer in case of respiratory commitment. They have the disadvantage of causing extrapyramidal adverse effects –especially when the patient is taking another neuroleptic agent, such as antiemetic (metoclopramide)-, or akathisis. The malignant neuroleptic syndrome and late diskynesia are very rare (189).

Tricyclic, heterocyclic and second-generation antidepressants can be efficient in anxiety that accompanies depression and in panic disorders. Their use is limited by their anticholinergic side effects and due to the latency time until their beneficial effects starts to be felt.

Opioids are useful to alleviate anxiety associated with dyspnoea or pain (163).

Summary of evidence

1+	No RCTs have been found on anxiety therapies in patient in the EOL (198).

Recommendations

D	The treatment of anxiety requires an individual assessment of the patient in EOL that includes the possible triggering causes, their adaptive state, the stage of the disease, associated treatments and the patient's preferences.
D	The psychological support measures for the patient and family are the first thing that must be provided after the individual assessment.
D	Pharmacological treatments are recommended when the psychological support is not sufficient. BZD can be used, preferably those with short or intermediate action.
√	In the case of anxiety associated with depression, delirium, dyspnoea or intense pain, tricyclic antidepressants, haloperidol or opioids, respectively can be used.

6.5.4. Depression

Depression is up to three times more frequent in patients in PC than in the general population. In the different series it varies between 3% and 77% of cancer patients, between 10% and 82% of HIV-AIDS patients; in patients with COPD or heart failure it can reach 70%, and in the cases of renal failure up to 50% (79) (see table 2). Sadness and depressed mood are normal responses in patients who are facing death. These emotions may be manifestations of an early bereavement to the loss of one's own life, their health, loved ones and independence (189).

Depression is not a normal state in the end-of-life phase, but an illness that complicates already existing illnesses and which is not diagnosed or treated as it should be (197).

The diagnosis of depression in PC is especially problematic. The manifestations of the illness and of its complications and side effects of the medication can make diagnosis difficult (203).

This can contribute, among other causes, to the fact that many physicians do not detect the depression of their patients, so the patient's emotional state must be monitored on a regular basis (204).

The formulation of a question: «Have you been depressed most of the time over the last two weeks?» has proven efficient to detect depression in the EOL (205).

The best tool to diagnose depression in these patients is a clinical interview, applying the modified DMS-IV criteria, based on emotional and cognitive symptoms rather than on somatic symptoms, which are very frequent due to the actual illness (tiredness, weight loss, etc.) (189; 205).

It is important in these patients to differentiate the genuine depressive disorder of normal bereavement from the adaptative disorder with depressed mood (197). Depression in palliative patients is important because it worsens their quality of life and that of their close friends and relations, and because it is an important risk factor of suicide and of request for an early death (206).

The DSM-IV criteria for depression diagnosis are (183):

A) Presence, during a 2-week period, of five or more of the following symptoms[7], which represent a change from previous functioning; at least one of the symptoms must be depressed mood or loss of interest or pleasure.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).
   2. Marked diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

[7] The symptoms clearly due to medical illness are not included, or delirious ideas or hallucinations that are not congruent with the mood.

3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor unease or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproaching guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B) The symptoms do not meet criteria for a mixed episode.

C) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning of the individual.

D) The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Expert opinion 4

The following are risk factors for depression being suffered by patients with cancer (189):

- Certain types of cancer: cancer of pancreas, primary or metastatic cancer of the central nervous system
- Family or personal background of having suffered depression.
- Pain.
- Degree of impairment.
- Stage of baseline illness.
- Treatments: corticosteroids, chemotherapy (vincristine, vinblastine, asparaginase, intrathecal methotrexate, interferon, interleukins), amphotericin B, total brain radiation.
- Endocrine-metabolic complications of the central nervous system.
- Paraneuroplastic syndromes.
- Loss of consciousness and low level of spiritual well-being.

Research about depression in the end-of-life phase has been mainly carried out on patients with cancer, HIV-AIDS and older people. Little is known about its

epidemiology in advanced phases of diseases of the heart, lung, liver, kidney and neurodegenerative illnesses. Most of the studies are small and with considerable methodological defects. Therefore, the recommendations are derived from expert opinions and from extrapolations from other population groups.

A low threshold must be established to start to treat depression in patients in PC. The first step is to control the pain, when this exists (197).

Expert opinion 4

Different systematic reviews have studied the pharmacological and non-pharmacological treatments in patients with cancer (203; 207). Due to the heterogeneity in the results, the publications present results without meta-analysis.

SR of RCT 1+

With respect to non-pharmacological therapy, the review of the AHRQ is based on three previous SRs; some of them include patients with cancer, but without a depression diagnosis (the appearance of this is one of the result variables assessed).

The interventions are based on psychological counselling and support by different professionals, social support, relaxation and group therapy. On the whole, the interventions are moderately efficient. It is not known which type of professional or format (group or individual) is associated with the best results.

The Rodin review (207) was based on four individual studies that included patients with depression diagnosis. The interventions included psychotherapy with or without relaxation, counselling programmes (information with participative feedback with experts) and organised intervention by nurses with multiple components (support and coordination sessions with the general practitioner). Only the psychological counselling programmes and the intervention organised by nurses were efficient.

In short, non-pharmacological interventions provided by the team caring for the patient (psychiatrist, psychologist, nursing staff, social worker and primary health care physician) can be sufficient in certain situations, depending also on the availability of means (professional profile, knowledge and skills, available time, etc.) and on the seriousness of the depression (203; 207).

There are no controlled studies about the efficiency of supplementary or alternative therapies in the treatment of depression in cancer patients (203).

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TAD) are efficient in the treatment of depression of cancer patients.

SR of RCT 1+

The Rodin review (207) included seven RCTs lasting from 10 days to 8 weeks, of variable quality, using mianserin (20-60 mg/day), fluoxetine (20 mg/day), paroxetine (20-40 mg/day), amitriptyline (75-150 mg/day) and alprazolam (1.5 mg/ 12 hours).

The AHRQ review (89) included nine studies (five shared with the Rodin review) and provides data about the efficiency of corticosteroids (methylprednisolone) and of desimipramine.

Overall, neither reviews show differences between the different groups of antidepressants. The individualised evaluation of the symptoms of each patient with the profile of side effects of the antidepressants and the possible interactions determine the choice of antidepressant.

The authors of the reviews recommend SSRIs as first choice due to their better profile of side effects (207). In general, patients in EOL tolerate paroxetine and sertraline better (197). Trazodone has a sedative effect that may limit its use in these patients (203).

Expert opinion 4

It takes weeks for the SSRIs and the TAD to start their action. Psychostimulants, such as dextroamphetamine, methylphenidate, modafinil and pemolin may produce a quicker response (even in the first 24 hours) and they are well tolerated (208). Therefore, in patients whose life expectation is limited to a few weeks, it is possible to begin with a psychostimulant (189; 197). Over the last few years several new antidepressants have been introduced, but they have not been assessed in this group of patients.

Pharmacological treatment of depression requires a meticulous assessment of the treatments the patient receives due to the risk of interactions and increase of side effects. The antidepressant treatment must be started at gradual doses in patients who receive drugs with sedative effects such as opioids; the association of SSRI with tramadol fosters the risk of convulsions.

Expert opinion 4

Although there are no controlled studies, most experts recommend a strategy that combines support psychotherapy, education of the patient and family and the administration of antidepressants (197; 209).

Assessment and treatment of the suicide risk

The risk of suicide in patients with cancer is up to 10 times greater than in the general population (210). Suicide risk factors include: non-controlled pain, advanced illness, male gender, depression, despair, delirium, previous psychopathology and abuse of substances, family or personal history of suicide attempts, advanced age (189) or social isolation.

Suicide thoughts are very frequent in patients with cancer in advanced phases (up to 45% of them present them), but they are usually fleeting and are associated with feelings of loss of control and anxiety about the future (197). However, some patients (up to 8.5% in a small prospective study) have persistent thoughts and a dominant desire to die quickly, and they also have a lethal plan: the immense majority of them suffer major depression and have a major risk of suicide (189). So, to reduce the suicide risk it is essential to identify the major depression, such as despair, which is an even stronger predictor than depression (189).

It is important to identify the cause of despair, which are frequently badly controlled symptoms (pain) and feelings of abandonment (189). The steps to assess suicide thoughts of patients in the EOL are summed up in table 19.

Table 19. Assessment of suicide thoughts in patients in the EOL (197)

Examine the reasons why the patient wants his of her life to end now. • Explore the meaning of his or her wish to die.	Expert opinion 4
Assess the control of physical symptoms and pain. • Is there a untreated or incorrectly treated pain that contributes to their desire to die ? • Is there a untreated or incorrectly treated symptom that contributes to their desire to die? • Are there fears about the death process that contribute to their desire to die? • Are they suffering adverse effects of drugs that can be alleviated?	
Review the patient's social supports. • Has there been a recent loss, conflict or rejection? • Are there new fears of abandonment or economic problems? • Who has the patient spoken to about the suicide plan? • What do these people think about that plan?	
Assess the patient's cognitive state. • Is there a cognitive deficit? • Are there new neurological signs or symptoms? • Does the patient understand his or her illness, its consequences and the consequences of suicide? • Is the patient's judgement distorted by despair or by other depression symptoms?	
Assess the patient's psychological state. • Does the patient suffer from anxiety, depression, delirium or any other untreated or deficiently treated psychiatric disorder? • How is the patient coping with the loss of control, dependence, uncertainty and bereavement?	
Explore their religious, spiritual and existential concerns. • Is there any unsolved or pressing question or concern in these areas?	

Establishing a therapeutic relationship is the basis for working with patients with a suicide risk. Talking of the suicide does not make it easier to occur; just the opposite: it legitimises the patient's concerns and enables him or her to describe their fears and feeling, increasing their feeling of control (197). Strategies to prevent suicide in cancer patients (211):

- Aggressively control underlying symptoms, especially pain. If necessary resort to sedation.
- Limit access to potentially lethal drugs, if necessary.
- Maintain frequent contact visits when the suicide risk and symptom control will be re-assessed, providing the drugs necessary until the next visit.
- Use drugs that work rapidly to alleviate psychological distress (e.g. a benzodiazepine for anxiety or a stimulant for asthenia).
- Avoid letting the patient spend long periods of time alone.
- Mobilise the whole family and social support network.
- Carefully assess the patient's psychological responses at each crisis point over the course of the disease.
- Consult a psychiatrist.

Summary of evidence

1+	Non-pharmacological therapies are efficient in slight to moderate depression of patients in PC (203; 207).
1+	Tricyclic antidepressants and SSRIs are efficient in the treatment of depression in patients in PC (203; 207).
2+	There are groups of patients in PC with a greater suicide risk (189).
3	Psychostimulants, such as methylphenidate, improve depressive symptoms in cancer patients and they have a quicker response than antidepressants (208).

Recommendations

D	The initial assessment of depressed patients in PC includes: identifying and addressing potentially treatable causes, evaluation of adverse effects and interactions of previous pharmacological treatments and estimation of the possible risk of suicide.
B	The initial therapy of depressed patients in PC includes psychosocial structured interventions, including psychotherapy by the personnel of the care team, and, if necessary, by specialised personnel within a structured programme.
B	If necessary, antidepressant drugs can be used (SSRI or tricyclic), bearing in mind their pharmacological properties, other drugs the patient receives and his or her symptom profile at each given time.
D	Psychostimulants, such as methylfenidate, can be used as an alternative to tricyclic antidepressants and SSRI, above all when a rapid start of the antidepressant effect is required or in cases with very short life expectancy.

6.6. Digestive symptoms

The questions that are going to be answered are:

- What are the most suitable measures for preventing and treating mucositis in people in EOL?
- What is the most suitable treatment for dry mouth?
- What are the most appropriate measures for preventing and treating oral candidiasis?
- What is the most suitable treatment for dysphagia?
- What is the most suitable treatment for nausea and vomiting?
- What is the most suitable treatment for constipation?
- What is the most suitable treatment for diarrhoea?
- What is the most suitable treatment for intestinal obstruction?
- What is the most suitable treatment for ascites?
- What is the most suitable treatment for hiccups?

6.6.1. Mouth care

Expert opinion 4

Mouth care is a very important aspect in patients in EOL. Lesions and complications are frequent and they have a great influence on the patient's well-being. It is important to try to prevent oral problems via good hygiene and hydration, as their consequences affect not only the correct diet and hydration of the patient, but also aspects relating to communication and social relations (212).

The purposes of good oral hygiene are:

- Maintain lips and oral mucosa clean, soft and without lesions as much as possible.
- Eliminate tartar and remains.
- Prevent oral infection, periodontal disease, tooth decay and halitosis.
- Alleviate pain and distress and increase or maintain oral intake.
- Prevent damage that may cause anti-neoplasia treatments.
- Minimise psychological distress and isolation and foster family involvement.
- Maintain the patient's dignity, also during the last moments.

A regular examination of the oral cavity by the actual patient is necessary, and it is advisable to instruct him or her about mouth care and hygiene (frequent brushing with adequate material) including dental prosthesis. Many of the commercial mouthwashes contain irritant products such as alcohol, lemon and glycerine, which are harmful in the case of irritation of the oral mucosa.

6.6.2. Mucositis

Most patients who receive radiation therapy or chemotherapy suffer mucositis as a side effect of the treatment. *Mucositis* is an inflammatory reaction that appears in the form of erythaema or ulcerations and may be accompanied by xerostomia and changes in the taste sense. It is a pathology that affects the patients' quality of life and may prolong hospital stays and interfere with the administration of treatments.

It appears 5 to 7 days after the treatment, depending on the dosage and type of chemotherapy. It is especially frequent with 5-fluorouracil (5-FU) and metotrexate. It is much more frequent in haematological neoplasia than in solid tumours (212).

There are very few RCTs about its treatment or prevention. Most of the studies that assess interventions in mucositis assess the improvement via scales and according to the decrease in pain. The most commonly used scale is the WHO scale, which defines the seriousness with a score of 0 to 4:

0 no signs of mucositis

1 erythaema or irritation

2 ulceration and eating capacity

3 ulceration and eating limitation

4 ulceration with haemorrhage and necrosis

SR of RCT 1+

The limited evidence about the prevention and treatment of this problem has been studied in two Cochrane SRs (213; 214) and in a recent specific CPG on the topic (215). There are discrepancies in the selection and assessment of evidence between the CPG and the SR.

The SR on prevention assessed 71 studies with 5217 patients. The studies are performed with patients treated with radiation therapy (radiation dose between 60-74 Gy) or high doses of chemotherapy. 51% are in head and neck tumours; 12 RCTs in patients submitted to bone marrow transplant.

The quality of the RCTs was very variable. Of the 29 interventions analysed, 10 showed some benefit.

The pharmacological measures that showed some positive results in at least two RCTs were amifostin, antibiotic tablet or paste and hydrolytic enzymes. Ice chips were effective in patients who receive chemotherapy with 5-FU.

Amifostin produces a slight benefit in the prevention of moderate and serious mucositis [RR 0.84 (IC 95%: 0.75-0.95) NNT of 10 (IC 95%: 2-33)] for a prevalence of mucositis of 60% in the control group. The hydrolytic enzymes (papain, trypsin, chymotrypsin) are administered orally and decrease moderate and serious mucositis, [RR 0.52 (IC 95%: 0.36-0.74)]. The NNT for prevalence of mucositis of 60% is 4 (IC 95%: 3-6).

Antibiotic paste (combination of polymyxin, tobramycin and amphotericin) also showed a moderate benefit in prevention of mucositis induced by radiation therapy, but the studies present a high bias risk (215; 216).

The ice chips prevented mucositis at all levels [RR 0.63 (IC 95%: 0.44-0.91)] and an NNT of 5 (IC 95%: 3-19).

RCT 1+

Other interventions that show some benefit in one single RCT are benzydamine, calcium phosphate, honey, povidone and zinc sulphate. All of them administered locally in the form of pastes or mouthwashes. The CPG recommends the use of benzydamine to prevent mucositis induced by radiation therapy (215).

RCT 1-

Some other studies were made after the SR. Oral glutamine (217) decreased the incidence of oral mucositis (two or more on the WHO scale), 38.7% vs. 49.7% (p = 0.026), and also serious mucositis (three or more), 1.2% vs. 6.7% (p = 0.005), in patients with breast cancer receiving treatment with chemotherapy with antracyclin. The recent CPG on this topic does not recommend this option due to its toxicity (215).

Another study, with few patients and non-masked assessment, obtained favourable results for palifermin (218). The CPG limits this latter drug to patients who receive treatment with high doses of chemotherapy and radiation therapy prior to a bone marrow transplant (215).

The decision to use preventive pharmacological treatment depends on the type of tumour and on the regime of radiation therapy or chemotherapy used (215).

SR of RCT
1+

The Cochrane review (214) on the treatment of oral mucositis in cancer patients receiving treatment with radiation therapy or chemotherapy included 26 RCTs, with a total of 1353 patients. Its objectives were to verify the effectiveness of treatments to improve or eradicate mucositis or stop the pain associated with it. 10 RCTs involved patients receiving bone marrow transplants, and 7 were on patients with head and neck cancer.

There is weak and contradictory evidence (only one test per intervention and with bias risk) that mouthwashes of allopurinol, granulocyte growth stimulating factors, immunoglobulins and extracts of placenta can be beneficial in the improvement or eradication of mucositis. The CPG recommends not using the granulocyte growth stimulating factors or chlorhexidine; the latter can be harmful (215).

There is no evidence that analgesia controlled by the patient is better to control pain than the continuous infusion method; however, the quantity of opioids used per hour and duration of the therapy are less in the first case.

There is weak evidence that analgesia based on pharmacokinetics reduces pain more than analgesia controlled by the patient, but a greater quantity of opioids is used.

Summary of evidence

1+	The treatments that offer some positive results in the prevention of mucositis in at least two RCTs are amifostin, antibiotic paste or tablet and hydrolytic enzymes. Ice chips are effective in patients who receive chemotherapy with 5-FU. Benzydamine, calcium phosphate, honey, mouth care, povidone and zinc sulphate prove to be effective in one single RCT (213) (217).
1+	There is contradictory evidence that allopurinol mouthwashes, local granulocyte growth stimulating factors, immunoglobulins and placenta extracts are beneficial to improve or cure mucositis (214).
1+	The quantity of opioids used per hour and the duration of the therapy with analgesia controlled by the patient are less than with continuous infusion (214).

Recommendations

D	Preventive pharmacological treatment must be indicated in agreement with the risk of developing mucositis. This risk is based on the clinical situation and on the modality and dosage of the treatment (radiation therapy or chemotherapy).
B	Prevention via drugs or local measures (hydrolytic enzymes, ice tablets, benzydamine, zinc sulphate) or parenteral (amifostine) can be carried out in selected cases.
B	There is not sufficient evidence to recommend the treatment of mucositis with mouthwashes of allopurinol, granulocyte growth stimulating factors or immunoglobulins, so the basis of the treatment is careful hygiene of the mouth and analgesics.
A	Analgesics controlled by the patient can be used to reduce the dose of morphine in the treatment of pain caused by mucositis.

6.6.3. Dry mouth (xerostomia)

Xerostomia is a subjective feeling of dry mouth that is not always accompanied by a detectable decrease in the production of saliva.

It is a very frequent symptom in patients in EOL. In a study on cancer patients in advanced stages, 88% mentioned medium intensity xerostomia (219). Its repercussions on the quality of life are important (220).

The absence of saliva increases ulcerations, candidiasis and infections. It also makes feeding more difficult and causes an unpleasant feeling for the patient.

There are several causes and they can foster each other: treatment with radiation therapy in head and neck tumours, medication, dehydration and psychological causes, such as anxiety and depression.

It is important to maintain the advice about mouth care commented in the previous section.

SR of RCT 1+

A systematic review in patients who suffered xerostomia after having received radiation therapy for head or neck cancer concludes that the treatment that has proven to be efficient is oral pilocarpine at doses of between 5 and 10 mg (221). According to data included in the meta-analysis an improvement in the xerostomia is observed [RR 1.83 (IC 95: 1.34-2.49)].

These data have been confirmed in a recent Cochrane review also on patients receiving treatment with radiation therapy (222).

The most frequent side effect was the increase in perspiration, which is related to the doses. Between 21 and 55% experienced this adverse effect (in the placebo group between 5 and 10%). The treatment abandonment rate due to perspiration is between 0 and 29%.

The authors comment as a limitation that pilocarpine has only proven its utility in patients treated with radiation therapy.

The pre-existence of the salivating function must be verified and there must be no contraindications to pilocarpine (although no serious side effects were observed, asthmatic patients or patients using beta-blockers were excluded from the studies).

SR of RCT 1+

A subsequent review (223), which included a broader spectrum of patients, also recommends the use of 5 mg pilocarpine three times a day (it can be increased to 10 mg) in individuals with xerostomia after treatment with radiation therapy. The most frequent side effects are: perspiration, rhinitis, digestive and urinary disorders. The treatment is contraindicated in patients with gastric ulcer, uncontrolled asthma, high blood pressure or in treatment with beta-blockers.

A recent study, included in this review, with pilocarpine mouthwashes in healthy individuals, shows promising results (increase of salivation with no side effects), but more studies are required.

The administration of 30 mg cevimeline three times a day is also effective for xerostomia in the Sjögren syndrome (223), although this drug is not marketed in our country.

There is no evidence that acupuncture (223) helps improve the symptoms in patients with xerostomia, nor of other external treatments, such as mouthwashes. **SR of RCT 1+**

A correct mouth hygiene and the use of salivation stimulators such as chewing gum, fruit (such as pineapple), ice and the use of artificial saliva (such as methylcellulose) can be useful in some cases, although the evidence about their efficiency is limited (212). **Expert opinion 4**

Summary of evidence

1+	Oral pilocarpine (5-10 mg/8 hours) is efficient in the treatment of xerostomia. It produces side effects due to its cholinergic action (perspiration, rhinitis, urinary disorders) (221-223).

Recommendations

D	In patients with xerostomia, salivation stimulants, ice or artificial saliva can be used as well as mouth hygiene.
A	Pilocarpine is indicated if pharmacological treatment of the xerostomia is required, bearing in mind its benefit and the possibility of side-effects.

6.6.4. Candidiasis

Candidiasis is the most frequent mycotic infection in cancer patients; 27% of patients admitted into oncology services present candidiasis with clinical symptoms and, in immunodepressed patients (220), candidiasis can be the origin of systemic dissemination.

Candidiasis can appear, above all, as a consequence of immunosuppressor treatments (chemotherapy and radiation therapy) or in HIV-AIDS; but it is also frequent in non-cancer patients as a result of antibiotic treatments, corticosteroids, deficient mouth hygiene, etc. (224).

There are few RCTs outside the context of the treatment of candidiasis produced by chemotherapy and radiation therapy, the majority carried out on patients with AIDS.

There is consistency about the efficiency of external treatments (nystatin, miconazole and clotrimazole) and oral treatments (itraconazole and fluconazole) (225; 226). Fluconazole is more effective than nystatin; there are no comparisons between miconazole and clotrimazole with oral treatment (225; 226).

The possibility of administering miconazole in one single dose, rather than five doses of clotrimazole should be taken into account when choosing the treatment.

If patients in PC are going to receive treatment with chemotherapy, the need for prophylaxis with antifungal agents may be posed. **SR of RCT 1+**

A Cochrane review addressed the prevention of candidiasis in patients with cancer who received chemotherapy or radiation therapy (227). It included 28 trials with 4226 patients.

Many trials are carried out on patients with neutropenia or with a high risk of suffering it due to the chemotherapy used, as 18 of the RCTs were on patients with leukaemia.

There is solid proof derived from RCTs that total absorption (fluconazole, ketoconazole and itraconazole) or partial absorption (miconazole and clotrimazole) antimycotics in the gastrointestinal tract (GI) prevent oral candidiasis in patients receiving treatment for cancer.

Seven trials with 1153 patients that compared two total absorption drugs compared with placebo or non-treatment, show an RR of 0.47 (IC 95%: 0.29 to 0.78%), which means an NNT of 9 (IC 95%: 7 to 13) in populations with an incidence of 20% in the control group.

Four trials with 292 patients compared partial absorption drugs in the GI tract with placebo and it was observed that these drugs also prevented oral candidiasis [RR 0.13; (IC 95%: 0.6 to 0.46)].

The drugs that are not absorbed in the GI tract (amphotericin B, nystatin or chlorhexidine) have not proven efficient in the prevention of candidiasis.

The prophylaxis is carried out on receiving treatment with radiation therapy or chemotherapy and the studies last from between three and six weeks (see table 20).

Table 20. Drugs for the prevention of candidiasis

Drug	Dose
Fluconazole Ketoconazole Itraconazole Miconazole	50 mg/12 hours 400 mg/day 100 mg/12 hours 500 mg/6 hours
Clotrimazol*	10 mg dissolved and swallowed /8 hours

* Presentation not available in Spain.

There is another Cochrane review (228) about the treatment of candidiasis in patients treated with chemotherapy or radiation therapy. There are not many RCTs about this question and the quality of those found is low and they do not include the most commonly used antifungal agents in our setting. There is weak evidence that ketoconazole can eradicate oral candidiasis and that clotrimazole at 50 mg dose is more effective than at 10 mg. Fluconazole proved to be more effective than nystatin in one of the RCTs include in the SR. **RS de ECA 1+**

In one RCT ketoconazole proves more effective than the placebo [RR 3.61 (IC 95%: 1.47-8.88)] and in another RCT clotrimazole is more efficient at 50 mg than at 10 mg doses [RR 2 (IC 95%: 1.11 to 3.6)].

Before taking a decision with respect to the treatment, the hepatic toxicity of ketoconazole must be taken into account.

Summary of evidence

1+	External treatments with miconazole, clotrimazole and nystatin and oral treatments (fluconazole and itraconazole) are efficient in the treatment of candidiasis in patients in PC.
1+	Total absorption drugs in the GI tract (fluconazole, ketoconazole, itraconazole) are effective in the prevention of oral candidiasis in patients with neutropenia or a high risk of suffering it, who are going to receive chemotherapy or radiation therapy (227). Partial absorption drugs (miconazole, clotrimazole) in the gastrointestinal tract are also effective in preventing oral candidiasis (227). The drugs that are not absorbed in the gastrointestinal tract (amphotericin B and nystatin) have not proven to be efficient in the prevention of oral candidiasis (227).
1+	There is weak evidence that ketoconazole can eradicate oral candidiasis in patients treated with chemotherapy (228).
1+	There is weak evidence in favour of 50 mg doses of clotrimazole as opposed to 10 mg in the treatment of candidiasis produced by chemotherapy (228).

Recommendations

B	Candidiasis not directly related with radiation therapy or chemotherapy can be treated firstly with external use antifungal agents (preferably miconazole or clotrimazole) and, if necessary, oral antifungal agents (itraconazole and fluconazole).
A	Treatment with ketoconazole, fluconazole and clotrimazole (50 mg) can be used in cancer patients with oral candidiasis after immunosuppression treatment.
A	Antifungal agents that are totally or partially absorbed in the gastrointestinal tract (fluconazole, ketoconazole, itraconazole, miconazole and clotrimazole) are the drugs of choice to prevent oral candidiasis in cancer patients with neutropenia or a high risk of suffering from it, who are going to receive treatments with chemotherapy and radiation therapy.

6.6.5. Dysphagia

Dysphagia can occur in patients in EOL due to different causes that affect the swallowing mechanism.

Mucositis and xerostomia affect the bolus chewing and preparation phases. Tongue disorders interfere in the oral swallowing phase, whilst the pharyngeal and oesophagus phases change due to the processes that affect these areas (tumour invasion).

There is little evidence about the treatment of dysphagia in general, as it depends on the treatment of the underlying cause.

Furthermore, dysphagia may be due to the affection of the nervous structures involved in swallowing either due to vascular, or neurological problems, or treatment effects (surgery, radiation therapy, etc.) (229).

The treatment requires individualised evaluation aimed at determining and, if possible, treating the responsible cause (see sections on mucositis and xerostomia). **Expert opinion 4**

Some general measures can be used aimed at favouring swallowing, such as adequate hydration, a soft diet adapted to the patient's preferences or use of thickeners (229).

In the case of obstructive problems, radiation therapy can reduce the size of the tumour and the corticosteroids decrease the peritumoural oedema (oesophagus, pharynx, larynx, etc.) (dexamethasone 8 mg/day oral or 4 mg parenteral) (229). **Case series 3**

The palliative treatment of dysphagia due to oesophageal primary tumours is not addressed in this CPG, as it requires specialised techniques, such as endoscopic dilation, brachytherapy, placement of stents by endoscopic route or treatment via endoscopic laser (230).

In cases of dysphagia due to obstructive components that do not respond to any measure, feeding via nasogastric tube, gastrostomy or jejunostomy can be evaluated. **Expert opinion 4**

Summary of evidence

4	There is little evidence on the treatment of dysphagia as a general symptom as it depends on its aetiology (229).

Recommendations

D	The treatment of dysphagia requires a personalised evaluation to identify and, if possible, treat the different causes involved.
D	The diet must be adapted to the clinical characteristics of the dysphagia. A soft diet is recommended, in agreement with each patient's tastes. In the case of dysphagia due to liquids, thickeners can be used.
D	A short cycle of corticosteroids can be tried in the case of obstructive dysphagia due to tumour invasion.
D	The team, the patient and his or her carers can decide on the use of a nasogastric probe or the execution of ostomies on the case of serious dysphagia that does not respond to the treatment and that prevents oral feeding.

6.6.6. Nausea and vomiting

Nausea and vomiting occur in 6 to 68% of cancer patients and the percentages vary between 30 and 50% in patients with HIV-AIDS, cardiac or renal failure(79) (see table 2).

The mechanism involved in the appearance of nauseas and vomiting is complex and involves the nervous and gastrointestinal systems. It can occur due to direct stimulation of the vomiting centre (metabolic alterations, opioids), endocranial hypertension (primary or metastatic tumours), gastrointestinal and vestibular disturbances, etc. Nausea and vomiting are the side effects of many of the treatments used in PC: analgesics (NSAID, opioids, etc.), antidepressants, neuroleptics, antibiotics and above all radiation therapy and chemotherapy. Both action mechanisms coexist in many situations. Chemotherapy can be an irritant of the digestive mucosa and act directly on the vomiting centre, for example.

A particular case is that of patients who suffer anticipatory vomiting, produced by situations that remind them of their experience of the appearance of vomiting and nauseas after a first cycle of radiation therapy or chemotherapy.

Two recent reviews (231;232) include evidence about nausea and vomiting. One of them (231) focuses on these symptoms within the context of patients who receive chemotherapy or radiation therapy, whilst the other (232) excludes them. There is a lot more literature about the prophylaxis and the treatment of nauseas and vomiting in the first case.

The specific oncology CPG recommends selecting the prophylaxis regime and treatment 24 hours after its administration depending on the risk of emesis of the drugs administered (233). **GPC 4**

Chemotherapy is classified into four categories according to the risk of emesis: high (>90%), moderate (>30% ≤90%), low (≥10% ≤30%), minimum (<10%) (233).

Radiation therapy categories correspond to the body surface radiated: high (>90%; the entire body), moderate (>60% ≤90%; upper abdomen), low (≥30% ≤60%; lower thorax, pelvis, cranial-spine) minimum (<30%; head and neck, limbs, breast) (233).

There are data for the prophylaxis in chemotherapy that guarantee the efficiency of dexamethasone (20 mg/day) (231; 234), 5HT3 antagonists (231; 235) (ondansetron* 16-24 mg/day) and metoclopramide (40-60 mg/day) (231). The 5HT3 antagonists and dexamethasone are more efficient than metoclopramide; the combination of dexamethasone with 5HT3 antagonists is more efficient than the monotherapy in patients with a low or moderate risk of emesis (235). **SR of RCT 1+**

Ant iemetics are used prior to the administration of chemotherapy during short periods of time; for example 5HT3 antagonists are administered in one single dose prior to chemotherapy.

Aprepitant, added to dexamethasone and to a 5HT3 antagonist increases the efficiency of the latter in patients with a chemotherapy regime with a high risk of emesis (236). **RCT 1+**

*** INFORMATION NOTE Spanish Agency of Medicines and Medical Devices (10th August 2012):**

Due the potential risk of arrhytmias, there are new recommendations for the use of ondansetron. The **maximum single intravenous dose** of ondansetron for chemotherapy induced nausea and vomiting is **16 mg.**

More information available at: http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_14-2012.htm

The cannabinoids nabilone, dronabinol (tetrahydrocannabinol) by oral route and levonantradol by IM route have proven more efficient than placebo and than other drugs such as haloperidol, domperidone or metoclopramide; but with a high frequency of multiple adverse effects, such as mood changes, sedation, paranoia or hypotension (237). This means that the patients who can benefit from the treatment must be carefully selected. These drugs are currently not marketed in our setting.

SR of RCT
1+

There is much less evidence about the prophylaxis of vomiting induced by radiation therapy. Apart from the extension of the radiated area, the dose administered per session must be taken into account.

One SR on 5HT3 antagonists in prophylaxis of vomiting caused by radiation therapy only found limited evidence in favour (238) with metoclopramide.

SR of RCT
1+

Another RCT not included in the SR shows that ondansetron was more efficient than a combination of dexamethasone and chlorpromazine in patients with a session of radiation therapy in lower hemibody. (239).

RCT
1+

A recent CPG recommends ondansetron, alone or combined with corticosteroids, for patients with a high risk of emesis. For the other categories, it recommends it alone, except for minimum risk category, for which prophylaxis is not recommended.

CPG
4

Approaching vomiting that takes place despite the prophylaxis recommended after chemotherapy or radiation therapy has not been studied as much. In these cases, the use of dexamethasone (4 to 8 mg/12 hours), metoclopramide (5-10 mg/8 hours) or domperidone (20 mg/6 hours) is recommended. Dexamethasone can be combined with either of the other two drugs (240-242).

Expert opinion
4

Nausea and vomiting not associated with specific oncological therapy were studied in the Glare SR (232), which included 22 studies (2 SR, 7 RCT and 12 non-controlled studies). Due to the heterogeneity of the studies, no meta-analysis was carried out. Metoclopramide is the most studied drug, proving to be more efficient than placebo and equally efficient as chlorpromazine.

RCT
1+

Corticosteroids are assessed in the cases of bowel obstruction (see specific section).

Haloperidol (231; 243) has not been assessed via RCT. It has proven efficient in case series, especially in nausea produced by opioids, renal failure or hypercalcaemia.

Case series
3

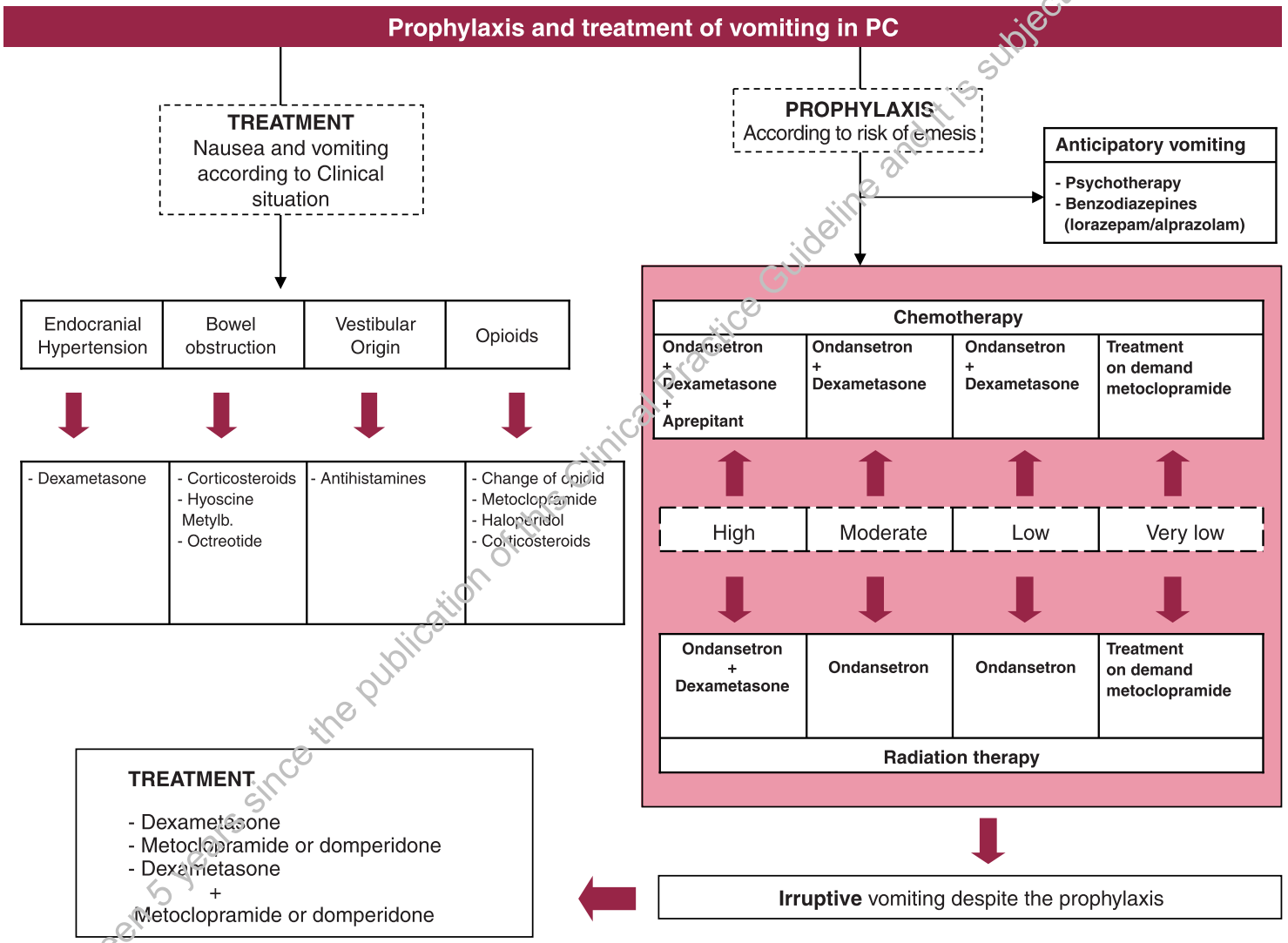
Concerning 5HT3 antagonists, an RCT found no differences between metoclopramide and ondansetron; in a second RCT, tropisetron, alone or added to corticosteroids, proved efficient in controlling nausea and vomiting in cases resistant to traditional treatment with metoclopramide or chlorpromazine.

RCT
1 +

Antihistamines are not backed up by RCT. The case series show positive responses when there are vestibular changes. There are no data about the efficiency of atypical antipsychotics.

There is little evidence about anticipatory vomiting. A recent review has been located (244). It is known that the incidence and intensity of vomiting in the initial

Figure 11. Prophylaxis and treatment of vomiting in patients in PC



treatment determine the appearance of the phenomenon, so correct prophylaxis can reduce its appearance. Patients under 50, family dysfunction and prior emotional disorder are also risk factors. There is consistent evidence about the efficiency of psychotherapy with behavioural techniques (systematic desensitisation) or relaxation techniques, which requires the availability of specialised personnel. There are some clinical trials with a reduced number of patients on whom the benzodiazepines (alprazolam 0.5-2 mg/day and lorazepam), added to the antiemetic treatment and psychological support, improved the anticipatory vomiting.

RCT 1+

The prophylaxis and treatment of vomiting in patients in PC are summed up in figure 11.

Summary of evidence

1+/3	Dexamethasone, 5HT3 antagonists and metoclopramide are efficient in the prophylaxis of vomiting in patients submitted to chemotherapy or radiation therapy (231-233; 239; 241).
1+	5HT3 antagonists and corticosteroids are more efficient than metoclopramide in the prophylaxis of vomiting of patients submitted to chemotherapy (231; 232). The combination of dexamethasone with 5HT3 antagonists is more efficient than monotherapy in patients with low to moderate risk of emesis (231).
1+	The combination of aprepitant with dexamethasone and 5HT3 antagonists is more efficient than the combination of the latter two in the prophylaxis of nausea and vomiting in patients with chemotherapy with a high risk of emesis (231; 234).
1+	The cannabinoids nabilone, dronabinol (tetrahydrocannabinol) by oral route and levonantradol by IM route have proven more efficient than placebo and than other drugs such as haloperidol, domperidone or metoclopramide; but with a high frequency of multiple adverse effects (mood changes, sedation, paranoia or hypotension) (237).
4	Dexamethasone (4-8 mg/12 hours), metoclopramide (5-10 mg/8 hours) or domperidone (20 mg/6 hours), and the combination of dexamethasone with any of the previous ones are efficient in the treatment of irruptive vomiting after treatment with chemotherapy or radiation therapy (240-242).
1+	Outside the context of patients treated with chemotherapy or radiation therapy, metoclopramide is efficient in the treatment of nausea and vomiting in the EOL (232).
3	Haloperidol produces an improvement of nausea and vomiting (243).
3	Antihistamines alleviate nauseas and vomiting produced by vestibular disturbances (232).
1+	Behaviour modification therapies are useful in anticipatory nausea and vomiting (244).
1+	Benzodiazepines (alprazolam and lorazepam), added to treatment with antiemetics and psychological support are efficient in anticipatory nausea and vomiting (244).

Recommendations

√	Treatment of nausea and vomiting in EOL patients requires a meticulous evaluation of the aetiology and the factors involved (endocranial hypertension due to tumour invasion, metabolic disorders, drugs, visceral affection, etc.) to be able to carry out personalised treatment.
D	The prophylaxis of nauseas and vomiting should be based on the risk of emesis in patients who receive chemotherapy or radiation therapy.
B	The association of 5HT3 antagonists (such as ondansetron) and corticosteroids is recommended in vomiting induced by chemotherapy with a moderate or low risk of emesis.
B	The association of 5HT3 antagonists, corticosteroids and aprepitant is recommended in vomiting induced by chemotherapy with a high risk of emesis.
D	Corticosteroids, domperidone, metoclopramide or combinations of corticosteroids with metoclopramide or domperidone can be used, depending on the intensity of the symptoms, in irruptive vomiting after treatment with chemotherapy or radiation therapy.
B	Metoclopramide is the treatment of choice in patients with nauseas and vomiting with no relationship with chemotherapy or radiation therapy. 5HT3 antagonists can be added to traditional therapy in the case of a limited control of symptoms.
B	Psychotherapy using behavioural techniques can be used in anticipatory vomiting. Alprazolam and lorazepam can be used as additional therapy to the counselling and to the psychotherapy.

6.6.7. Constipation

Constipation affects a large proportion of patients in PC (see table 2). In cancer patients this proportion can reach up to 65% and in renal failure 70%. Immobility, diet, some metabolic disorders, such as hypercalcaemia, and above all the use of drugs, such as opioids, explain this prevalence. In patients in EOL who receive opioids, constipation can be present in up to 87% of the cases (245).

The treatment patterns used in the general population with respect to food and physical exercise are difficult to apply in PC, so the use of laxatives is an almost compulsory need (246).

Expert opinion 4

However, the patient's general care plan must include sufficient intake of liquid, diet with fibre, mobilisation adapted to each patient and the anticipation of possible constipation produced by drugs (247).

The efficiency of laxatives has been studied in two recent reviews (245; 246). The Cochrane review examines the treatment in patients in PC, whilst the second focuses only on patients being treated with opioids.

There are many laxatives used in PC; however, only a few RCTs have studied their efficiency. Neither of the two reviews find any RCTs or cohort studies that assess enemas or glycerine suppositories, for example.

Laxatives can be classified according to their action mechanism:

- Bulking agents (methylcellulose, ovate plantain).
- Colonic stimulants (sen, sennosides A and B, bisacodyl, sodium picosulphate).
- Lubricants and emollients (docusate, mineral oils).
- Osmotics (lactulose, lactitol, magnesium salts, polyethylenglycol).

The Cochrane SR (246), based only on four RCTs (280 patients), finds moderate efficiency for lactulose, sen, dantron combined with poloxamer (not marketed in Spain) and magnesium hydroxide combined with liquid paraffin. **SR of RCT 1+**

The second (245) confirms the efficiency of the same drugs plus the efficiency of polyethylenglycol. No differences in efficiency or side effects have been found between lactulose and sen or polyethylenglycol. The patients' preferences and the team's experience of use determine the choice of laxative. **SR of RCT 1+**

Sufficient data have not been found to guarantee the efficiency of other laxatives commonly use in PC, such as magnesium salts alone, methylcellulose or sodium picosulphate.

Another frequent clinical situation that complicates constipation in patients in PC is faecal impaction (faecalomas), as it limits the quality of life of patients and their family members. It must be ruled out by means of a rectal examination before prescribing specific treatments for constipation. The use of laxatives administered by rectal route is recommended to treat faecal impaction,: suppositories (glycerine) or enemas (sodium citrate, phosphate) /247). Their use requires a correct analgesia of the patient. **Expert opinion 4**

Summary of evidence

1+	Lactulose, sen, polyethylenglycol, dantron combined with poloxamer and magnesium hydroxide combined with liquid paraffin are efficient in the treatment of constipation in patient in PC receiving opioids or not (245; 246).

Recommendations

√	The presence of faecalomas must be ruled out before prescribing treatment with laxatives.
A	The use of laxatives is recommended (sen, lactulose alone or associated with sen, polyethylenglycol, magnesium salts and liquid paraffin) together with an adequate diet (sufficient hydration and fibre) and adapted exercise.
B	The prescription of opioids must be accompanied by constipation preventive measures, including laxatives.
D	Laxatives by rectal route (suppositories or enemas) can be used in the case of faecal impaction.

6.6.8. Diarrhoea

Diarrhoea is less frequent than constipation in PC, especially in cancer patients. In some case series the percentage reaches 30%; in the case of HIV-AIDS up to 90% (79) (see table 8).

SR of RCT
1+

As in many of the digestive symptoms, the aetiology is multifactoral. The possible causes of diarrhoea in PC are described in table 21. One of the most common causes is the use of laxatives (247).

Table 21. Aetiology of diarrhoea in PC

- Laxatives
- Medication: antibiotics, NSAID, antiacids
- Chemotherapy (above all 5-fluorouracyl and irinotecan)
- Radiation therapy
- Malabsorption syndrome: sequelae of digestive surgery, pancreas carcinoma
- Tumours: digestive and carcinoid
- Gastroenteritis and other infections
- Intestinal obstruction
- Faecal impaction

The initial approach to patients with diarrhoea in PC is to identify the aetiology. Knowing the cause of the diarrhoea is especially important, as some therapies, such as the use of opioids, are contraindicated in infectious diarrhoeas. Other causes, such as toxicity induced by chemotherapy and radiation therapy, or malabsorption syndromes, require specific therapy.

Diarrhoea produced by chemotherapy, above all with some agents such as 5-fluorouracyl or irinotecan, requires a specific assessment and treatment. The toxicity of diarrhoea can be classified in agreement with the frequency of daily stools and the affectation of the general state (table 22). Degrees 3 and 4 exceed the aim of this guideline (consult reference (248)). Degrees 1 and 2 can be treated at the patient's home, so long as there are no systemic complications (fever, signs of infection, significant decrease of functional capacity, etc.).

Table 22. Classification of the seriousness of the diarrhoea produced by chemotherapy

	Degree				
	0	1	2	3	4
Patients without colostomy	None	Increase up to 3 dps/d	Increase between 4 and 6 dps/d or dps at night	Increase of 7 or more dps/d or need for parenteral hydration	Deterioration that requires intensive care or haemodynamic failure
Patients with colostomy	None	Slight increase in the colostomy content	Moderate increase that does not interfere with the patient's activities	Severe increase that interferes with the patient's activities	Deterioration that requires intensive care or haemodynamic failure
dps/d: stools/day					

After identifying the cause, the initial treatment is based on an appropriate diet with sufficient intake of liquids and salts to avoid dehydration (247).

Expert opinion 4

Opioids are the most commonly used drugs to treat diarrhoea in PC. Their use as analgesics can avoid the use of additional anti-diarrhoeal agents.

Loperamide is the anti-diarrhoeal agent of choice. It is also efficient in treating diarrhoea produced by chemotherapy and radiation therapy. The criteria used in the RCTs are variable and can reach 16 mg/day (249-253). The most common criterion consists of an initial dose of 4 mg, followed by 2 mg with each bowel movement until the intestinal rhythm becomes normal, but not exceeding 16 mg/day.

RCT 1+

In the case of refractory diarrhoea, the efficiency of somatostatin and octreotide has been assessed in a meta-analysis with some methodological problems (search limited to English, little description of the assessment of the articles included) (254). This publication included RCTs and case series; somatostatin was only used in three RCTs and none of them in patients treated with chemotherapy. The results show the efficiency of somatostatin and octreotide, although there was heterogeneity in the results. The results were homogeneous in patients with HIV-AIDS (less efficient). Octreotide was used in the form of progressive doses from 50 mcg by subcutaneous route up to 5000 mcg every 8 hours, lasting for 2 days to 33 weeks. The treatment lasted from 3 to 5 days in patients receiving chemotherapy.

SR of RCT 1+

This drug can also be used via subcutaneous infusion pumps. This indication is not approved in our country.

Summary of evidence

1+	Loperamide is efficient in the treatment of diarrhoea induced by chemotherapy and radiation therapy (249-253).
1+	Octreotide is efficient in the treatment of refractory diarrhoea (254).

Recommendations

D	The treatment of diarrhoea in PC requires the identification of possible correctable causes, the evaluation of the degree depending on the rate of bowel movements and the affection of the general state, and an initial treatment with diet and intake of appropriate liquids.
B	Loperamide is indicated when diarrhoea of non-infectious origin persists, including stages 1 and 2 produced by chemotherapy or radiation therapy.
D	Loperamide is indicated in cases until 12 hours elapse without bowel movement. In the case of radiation therapy, it is indicated for the time the treatment lasts.
B	Subcutaneous octreotide can be used (including the use of infusion pumps) in selected cases in the case of refractory diarrhoea.

6.6.9. Bowel obstruction

Malignant bowel obstruction (MBO) is frequent in patients in oncological PC, above all in the cases of digestive and gynaecological tumours. In colorectal cancer this may vary between 4.4% and 24%, in cancer of the ovary between 5.2% and 42% and in other advanced phase tumours between 3% and 15% (255).

Although the presence of tumours is the cause involved in the majority of the patients, other possible causes must be ruled out, such as adherences after surgery, faecal impaction due to constipation and pharmacological side effects, above all of opioids.

The therapeutic alternatives in MBO are surgery, endoscopic treatment and medical treatment. Normally, surgery consists in carrying out a palliative colostomy. Endoscopic treatment consists in the placement of self-expanding metal prostheses (stents).

The decision about surgical treatment is complicated. The benefits of the surgery must be carefully evaluated in terms of solving the obstruction, alleviating pain, relapse of the obstruction and quality of life. The patient's life prognosis and the surgical complications must be taken into account, as post-operatory mortality and subsequent complications are much higher in these patients (255). Table 23 shows a list of contraindications to surgery contained in a CPG on this subject (256).

Table 23. Contraindications to surgery in MBO

Absolute	Relative
• Metastatic cancer demonstrated by prior surgery • Intra-abdominal carcinomatosis that produces motility wdisorders • Palpable abdominal diffuse masses • Rapidly recurrent massive ascites following paracentesis	• Extra-abdominal metastases that produce difficult to control symptoms (e.g. dyspnoea) • Non-symptomatic extra-abdominal tumour extension • Serious general deterioration • Nutritional status with serious deterioration • Advanced age associated with cachexia • Prior abdomen or pelvis radiation therapy

Expert opinion

There is a Cochrane SR on surgery of MBO in gastrointestinal and advanced gynaecological cancer. This review did not locate any RCTs and it is based on 2058 patients from 24 retrospective studies and one prospective study. An improvement was obtained in 42% to 80% of the cases with recurrence of the obstruction in 10 to 50%. The peri-operatory mortality varied between 5 and 32%, with an important post-operatory morbility (wound infection, dehiscence, sepsis, fistula, thromboembolism, etc.). Post-operatory morbility is very frequent in these patients, varying in the different series between 9 and 90% of the cases (255).

SR of case series 3

Treatment via stents is a recent technique that is used both as a step prior to curative and palliative surgery. It consists in the endoscopic insertion by rectal route of a folded cylindrical tube that expands once in place and rechannels the obstruction. Only a few comparative studies have been carried out to date with other alternatives such as surgery.

A recent SR, without meta-analysis has studied the efficiency and complications of the technique in both situations (curative or palliative) (257). 88 articles were included, of which only 15 were compared with surgery, two of them RCTs. The others were 73 retrospective case series.

SR of RCT and case series 1+/3

Of the 1785 patients included, the stent was used with palliative intention in 762 (43%).

The quality of the information (methods to appraise the results, duration of the functional state of the stent, need for re-intervention, etc.) provided by the studies was poor. Table 24 includes a summary of the main results in the population with palliative intention.

Table 24. Results (% and range) of the placement of stents with palliative intention in MBO (257)

Results	Mean %	Range %
Prosthesis functioning at end of follow-through or death	90	53-100
Perforation	4,5	0-83
Replacement of new prosthesis	20	0-100
Postoperatory mobilisation of prosthesis	11	0-50
Obstruction	12	1-92

In the two RCTs included in the review, the stent had palliative intention and was compared with surgery. 52 random patients were included (but with no specification of the method) and the results appraisal was not blind (258; 259). The results regarding survival and recovery of oral feeding were similar in both groups, but the hospitalisation period was significantly less in the stent group. The obstruction was not complete in one of the RCTs (259).

RCT 1+/-

The medical treatment of MBO in patients on whom surgery has not been considered appropriate is aimed at alleviating symptoms, such as pain, nausea or vomiting. This requires treatment associated with antiemetic, analgesic and antisecretory drugs (256).

Expert opinion 4

Corticosteroids have been widely used in this indication based on their anti-inflammatory and anti-secretion effect. Feuer carried out a review on these drugs (260). He located 10 studies (only three RCTs) with 270 patients in all, who used intravenous corticosteroids (dose range equivalent to dexamethasone of 6 to 16 mg). He found there was a tendency towards an improvement of the obstruction but no significant difference was obtained. There were no effects on the mortality, either, or data about new obstruction episodes. The RCTs presented some methodological problems, such as accompanying treatments used and the loss of patients.

SR of RCT 1+/-

The recent review by Mercadante (261) studied any medical treatment: corticosteroids compared with placebo (same RCTs as the Cochrane SR) and octreotide compared with butylscopolamine (103 patients), added to standard support treatment. This last comparison included three RCTs with methodological problems in a population with worse prognosis than that of the corticosteroid RCTs. The doses used were between 0.3 and 0.8 mg/day of octreotide and 60 to 80 mg/day of butylscopolamine. The result variables considered were nausea and vomiting, pain, dry mouth, asthenia and anorexia. Octreotide proved to be more efficient in alleviating nausea, but with no differences in the other variables, including adverse effects. There is no approved indication in our country.

SR of RCT 1+/-

There are no comparisons between octreotide and corticosteroids.

Summary of evidence

1+	Surgery and the placement of stents are efficient treatments in selected patients with MBO (255; 260).
1+/-	Endoscopic treatment with placement of stent requires less hospitalisation time than palliative surgery (257).
1+/-	Corticosteroids present a non-significant tendency in the solution of symptoms in MBO, without achieving changes in mortality (261).
1+	Octreotide is more efficient in alleviating nausea and vomiting than butylscopolamine and equally efficient in the other variables, including survival in MBO (261).

Recommendations

D	Patients with MBO require an individual evaluation that bears in mind their functional situations, including surgical contraindications; the location of the obstructions; their preferences, the availability of surgical or endoscopic techniques or experience with them in the setting where the patient is treated.
C	Surgery and the endoscopic placement of self-expanding metal stents (SEMS) can be used in selected patients with MBO.
C	The medical treatment of bowel obstruction must include analgesics, antiemetics and antisecretory drugs. Corticosteroids and butylscopolamine can be used as additional therapy.
√	If there is a lack of response to the previous measures octreotide can be used.

6.6.10. Ascites

Ascites can occur in 15% to 50% of cancer patients (262). It is much more frequent in certain kinds of tumours, such as lung, gynaecological, pancreas or colon. Up to 20% of the cases are due to unknown neoplasia.

A recent SR studied the existing evidence on the measures used in practice: paracentesis, diuretics and peritoneovenous shunts (263). The SR did not locate any RCTs.

The findings are summed up below:

SR of different types of studies 2+/3

- **Paracentesis:** three case series and two cohort studies. They proved to be highly efficient in alleviating symptoms, but not side effects. The studies carried out evacuations of up to 5 litres. The routine administration of serum therapy or albumin does not seem to be efficient.
- **Diuretics:** one open ended trial, three cohorts and one case series. IV furosemide and spironolactone were assessed, either alone or combined with furosemide. Modest efficiency was achieved, but with possible alterations of ions and of the renal function.

  Spironolactone can be recommended alone or combined, at the doses used in non-malignant aetiology ascites.
- **Peritoneovenous shunts:** 21 case series and one non-controlled trial were found. Two types of shunts (Le Veen and Denver) were compared, which differ in the pressure they work at, though it was not possible to conclude which was better. The response for gastrointestinal neoplasias was worse and better for breast and ovary neoplasias. The measure proved to be efficient, but had frequent and serious side effects in 6% of the cases (obstruction, pulmonary oedema, pulmonary embolism, etc.), which meant that the patients, who can benefit from this measure, have to be very carefully selected.

Summary of evidence

3	Paracentesis, diuretics and peritoneovenous shunts alleviate the symptoms produced by the ascites.

Recommendations

D	Paracentesis can be used in the case of malignant ascites that requires symptomatic treatment.
D	Treatment with diuretics can be considered in very selected cases where the presence of high levels of renin is suspected, and in ascites due to advanced cirrhosis.
D	Peritoneovenous shunts can be considered in selected cases following the failure of the previous measures.

6.6.11. Hiccups

Hiccups are a respiratory reflex defined by the involuntary, sudden and spasmodic contraction of one of the sides of the diaphragm, followed by a sudden closing of the glottis, causing a peculiar and characteristic sound.

They are classified as acute (duration <48 hours), persistent (≥48 hours) or untreatable (>2 months).

There are no exact data about the prevalence of hiccups in PC patients, but in some cases it can lead to considerable suffering by the patient and family (229).

Hiccups can occur due to direct stimulation of the phrenic and vagus nerves and due to the action of the central nervous system. There are many causes that can act through these mechanisms, including abdominal or mediastinic tumour disease, multiple sclerosis, effects of treatments (gastric dilation, abdominal surgery, etc.), pharmacological side effects (corticosteroids, opioids, BDZ, etc.), intercurrent processes (pneumonia, pleuritis, etc.).

The fact that several action mechanisms can coexist in the same patient must be borne in mind.

The first measures in the treatment are aimed at inhibiting the hiccups reflex: forced apnoea, pharyngeal stimulation by different methods, such as a plastic catheter, massage of the soft palate, etc.

If the hiccups persist and affect the patient considerably, pharmacological treatment must be resorted to.

Lacking RCTs in PC patients, the literature includes many case series with experiences with different drugs. **Case series 3**

The most commonly recommended guidelines by different authors are included in table 25 (229; 264; 265). Some can be combined, as for example drugs that act on a central level such as baclofen or metoclopramide with omeprazol

Table 25. Drugs and dosage used to treat hiccups

Drug	Dose
Chlorpromazine	25-50 mg/6-8 hours
Metoclopramide	10 mg/6-8 hours
Baclofen	5-10 mg/12 hours (up to 20 mg/8 h if necessary)
Gabapentin	300-600 mg/8 h
Nifedipine	10-20 mg/8 h
Haloperidol	3 mg at night
Omeprazol	20 mg/day

Baclofen is the most studied drug, so it can be the first drug to be used in these cases. Some authors advise against chlorpromazine due to its adverse effects (229).

In cases where hiccups persist that do not respond to previous measures, the use of IV midazolam is indicated (229) before resorting to other surgical techniques that go beyond the objective of this CPG.

Summary of evidence

3	The response of patients with persistent or untreatable hiccups to non-pharmacological measures and to some drugs is variable (229).

Recommendations

D	Treatment of patients with persistent or untreatable hiccups requires a meticulous evaluation and the treatment of possible causes. If the hiccups persist, treatment with physical measures must be attempted.
D	Pharmacological treatment (baclofen, metoclopramide, haloperidol, nifedipine or gabapentin) can be used if necessary, bearing in mind the interactions and side effects in each case. Baclofen is the initial drug if there is no contraindication for its use. It can be used alone or combined with omeprozal.
D	In the case of untreatable hiccups, and following the failure of oral therapy, parenteral midazolam can be used.

6.7. Skin Care

The questions that are going to be answered are:

- What is the best way to prevent ulcers in people in EOL?
- What is the most suitable treatment for ulcers in people in EOL?
- What is the most suitable treatment for fungating wounds?
- What is the most suitable treatment for pruritus?

6.7.1. Prevention and treatment of ulcers

Skin problems are very frequent in people in EOL due to different reasons: malnutrition, dehydration, immobility, as well as those derived from treatments such as radiation therapy or chemotherapy, or the actual nature of the disease, as in the case of fungating wounds. In preventive aspects of pressure ulcers, the measures must be similar to those used in any patient, although in the treatment, the objectives must give priority to comfort over cure. It is important to take into account the impact of skin pathology on the perception of one's own image and its impact on the lives of the patient and his or her carers.

What is the best way to prevent ulcers in people in EOL?

Pressure ulcers (PU) are skin lesions that can affect the muscle and even the bone and are caused by a combination of factors including pressure, traction and shearing. The pressure/time relationship is a factor that determines their appearance. They can occur anywhere, although the most frequent places are bone protuberances (266).

Prevention is the essential tool of PU and in the case of patients in EOL, if they cannot be entirely prevented, it is important to delay their appearance as much as possible to minimise the impact on the patient's quality of life.

Relief of pressure is obtained by posture changes and when necessary, the use of devices for this purpose. The Cochrane review on this subject (267) concludes that the different foam alternatives rather than the standard mattress can reduce the incidence of PUs. The relative advantages of constant pressure and alternating pressure devices and of the different alternating pressure systems are not very clear. In general, the studies present methodological limitations, so it is a subject that requires further research.

SR of RCT 1++

Another review (268) respect to the prevention of PUs concludes that posture changes, special support surface, a good nutritional status and skin hydration are the best prevention strategies, but the quality of the RCTs is low in general.

SR of RCT 1+

Otherwise, skin care measures include: keeping it clean, dry and moisturized ; avoid wrinkles in the patient's clothing or in the bed, and do not raise the bed head by more than 30 degrees.

Expert opinion 4

Hyperoxyginated fatty acids have proven their usefulness in the prevention of PUs (269).

ECA 1+

What is the most suitable treatment for PU in people in EOL?

If pressure ulcers appear, despite the prevention measures, the treatment must be realistic in its objectives and accepted by the patient. The main objective is to minimise the impact of the PUs on the patient's quality of life, and if the measures implemented do not contribute to an increase in the patient's comfort, the treatment must be reconsidered.

SR of RCT 1+

To choose the correct dressing for each ulcer, it must be taken into account that there is no evidence that proves the superiority of one kind with respect to the other (266), so the stage of the ulcer, the objectives and the patient's comfort must be considered.

The ideal dressing must satisfy these conditions:

- Permit the absorption of any excess exudate from the wound surface.
- Provide a moist atmosphere for the wound.
- Be sterile, not permitting the contamination of the wound.
- Reduce pain.
- Be easy to put on and take off.
- Not cause allergic reactions.
- Not produce harm to the tissue when removed.
- Be impermeable to micro-organisms.
- Provide thermal insulation.

Pain, the control of the exudate and smell are very important for patients in EOL (220). The results of a study performed with this kind of patient (270) were positive, verifying the efficiency of a diamorphine gel to reduce the pain produced by PUs in patients of a hospice. The study is too small to be able to generalise the results. Given that diamorphine gel is still not marketed in our setting, these conclusions do not provide us with information of immediate practical utility; however, it is important for future research.

There are no data about the quality of life.

What is the most suitable treatment for fungating wounds?

A Cochrane review addressed the topic of external treatment of fungating wounds (271). This review located two studies: **SR of RCT 1+**

- One study on the external application of a 6% miltefosine solution.
- A second study on external metronidazole 0.8% in gel.

In the case of miltefosine, the time until the failure of the treatment was significantly greater in the intervention group (average 56 days, 8-324 range) than in the control group (average 21 days, 8-197 range).

In the study with metronidazole, a reduction of the smell is observed in the intervention group that has no statistical significance.

These trials included few patients, especially the metronidazole trial. They are also low quality, so no firm conclusions can be reached. There is weak evidence that miltefosine in 6% external solution can curb the progression of ulceration.

Summary of evidence

1+	The different special surface alternatives help prevent ulcers, compared with the traditional mattress (267).
1+	Hyperoxygenated fatty acids are efficient in the prevention of PUs (269).
4	Posture changes, the maintenance of the best possible nutrition and hygiene and skin hydration are appropriate care processes to prevent the appearance of the PUs (268).
1+	There is no evidence of the superiority of one type of dressing for the treatment of PUs. There is weak evidence that 6% miltefosine solution for external use can curb the evolution of fungating wounds (271).

Recommendations

D	The prevention measures of PUs include: changes in posture, adequate nutrition, not raising the head of the bed more than 30 degrees and maintaining adequate cleanliness and moisturizing.
A	Special support surfaces are recommended in patients with a high risk of developing PU.
A	The use of hyperoxygenated fatty acids is recommended in patients with a high risk of developing PU.
D	The type of dressing should be chosen depending on the stage and characteristics of the ulcer, on the objectives and patient's preference.
D	Metronidazole administered externally can be used to reduce the smell in fungating wounds.
B	6% miltefosine solution can be used externally to curb the evolution of fungating wounds.

6.7.2. Pruritus

This is a common symptom in patients in PC. It is estimated that it can be present in up to 27% of patients with tumours and up to 80% if these are cholestasis-induced. In patients with advanced renal failure it can reach 77% of the cases (average 55%) (272).

Pruritus is defined as an unpleasant feeling that induces scratching and which improves or stops when this is done. Its origin can be in the skin (dermatitis, scabies, etc.), neuropathic (due to lesions of afferent pathways of the nervous system: peripheral neuritis); neurogenic (due to mediators that act at central level, such as opioids, for example) and, finally, psychogenic.

The aetiopathogeny of pruritus is complicated and not sufficiently studied. There are different chemical mediators responsible for the appearance of pruritus (histamine, serotonin, cytokines, growth factors, prostaglandins, etc.). In some cases, it is present more as a mediator. Knowledge of this permits the best selection of pharmacological treatment.

For example, in cholestasis there is an increase of endogenous opioids, whilst in renal failure there are many mediators involved so anti-histamines are not a treatment of choice in the first case but they are in the second. Opioid antagonists may be useful in cholestasis and have shown conflicting results in renal failure (273).

Patients in PC can present skin aetiology pruritus due to primary dermatoses, some of them produced by radiation therapy or drugs (eczema, hives, mycosis, dry skin, etc.), or directly related to primary or metastatic tumours. Paraneoplastic syndromes, cholestasis, advanced renal failure stand out within generalised pruritus, as well as pruritus produced by some special types of haematological tumours such as polycythemia or Hodgkin's disease and drug-induced pruritus, especially opioids.

Dry skin is the most frequent cause of pruritus, as in the general population, so general skin care is especially important to prevent it.

Skin hydration and hygiene are especially important in these patients, using mild soap without detergent, moisturising and emollient creams.

Expert opinion 4

To treat pruritus, the underlying cause must be identified and treated first of all, with special emphasis on the drugs. However, there is a series of simple general measures which include: maintaining correct skin hydration, bathing with warm water and emollient agents, avoid alcohol and spicy food, cut nails, use cotton gloves at night, avoid heat and tight clothing, etc. (274).

The evidence about external agents is limited. Calamine lotion or powder with 0.25-2% menthol can be used. External corticosteroids can be used in cases of localised pruritus (274).

Phototherapy with ultraviolet rays can be used in advanced renal failure.

When the aetiology is a biliary obstruction, a biliary shunt can be considered. In opioid-induced pruritus the continuity of opioids must be appraised.

Just like the treatment of pruritus in the general population, few RCTs have been performed in PC. There are several narrative reviews that have examined the efficiency of the different treatments, with many contradictory conclusions. Most of the studies considered are case series with few patients and many of them are not specifically carried out in PC; for example, the RCTs performed on riphampicin in malignant cholestasis (275).

As a result, treatment with successive drugs is very often necessary, evaluating the individual response to the treatment.

Based on different reviews and studies (273-281), the treatments with an onset proposal and sequential order are summed up in table 26, bearing in mind the action mechanism and the efficiency.

RCT, case series, Expert opinion 1+/3/4

Table 26. Proposal for treatment selection according to pruritus aetiology

Cause	Pharmacological proposal
Cholestasis	1. Naltrexone 2. Androgens (methyltestosterone or danazol) 3. Riphampicin 4. Cholestyramine
Uraemia	1. Phototherapy 2. Antihistamines 3. Ondansetron 4. Mirtazapine 5. Thalidomide
Paraneoplastic syndromes	1. Paroxetine 2. Mirtazapine 3. Combination of 1 & 2 4. Thalidomide
Haematological neoplasias	1. Cimetidine 2. Paroxetine
Dry skin	1. External moisturizing, emollients 2. Antihistamines
Opioids	1. Replacement or rotation of opioids 2. Ondansetron
The treatment options are numbered to be used in the order in which they appear.	

Summary of evidence

2+/3	Different drugs have proved to alleviate pruritus in series of patients: naltrexone, antihistamines H1 and H2, ondansetron, androgens, thalidomide, mirtazapine (273; 274; 276-281).
1+	Paroxetine is efficient in alleviating non-dermatological pruritus in people in PC (278).
1+/-	Riphampicin is efficient in treating chronic hepatopathy pruritus (275).

Recommendations

D	Initially managing a person with pruritus consists in identifying and, if possible, specifically treating the underlying causes, with special emphasis on the drugs. Aggravating factors, such as alcohol, spicy food, heat, the use of tight clothing, the use of soap with detergents, etc. must be avoided.
D	General skin care must be provided, including sufficient moisturizing and prevention of injuries caused by scratching.
D	Pharmacological treatments will be administered if necessary depending on the origin of the pruritus (opioids, uremic, cholestatic, paraneoplastic, dry skin). Treatment may change depending on the therapeutic response, following the outline proposed in table 26.

6.8. Urinary Symptoms

The questions that are going to be answered are:

- What is the most suitable treatment for urinary urgency?

6.8.1. Urinary urgency

This is the pain that appears in the hypogastric area (suprapubic) and can be associated with other symptoms such as dysuria, nocturnal and urgent polyuria, as well as retention or incontinence (282). Its most common causes are summed up in table 27.

Table 27. Common causes of pain or urinary urgency in PC (282)

Infection of the urinary tract	Foreign body
• Bacterial, including tuberculous cystitis • Fungal (immunocompromised patients) • Urethritis • Genital herpes • Vaginitis	• Urethral or suprapubic catheter • Bladder stone
Anatomical	**Bladder instability**
• Pelvis mass • Urethra obstruction • Cystocele	• Idiopathic bladder spasm • Secondary bladder spasm: contractions in the area of the catheter, blood clots, tumours or infection
Neoplastic	**Inflammatory**
• Bladder tumour • Urethra tumours	• Idiopathic bladder spasm • Radiation therapy • Chemotherapy (cyclophosphamide) • Intravesical chemotherapy or immunotherapy for bladder cancer • Amyloid

Treatment of urinary urgency

There is no evidence about how to treat urinary urgency, so the recommendations are based on expert consensus (282). **Expert opinion 4**

The non-pharmacological treatment consists in insisting on regular urination habits, adequate intake of liquids and avoiding caffeine and alcohol.

The most commonly used drugs are included in table 28.

Table 28. Most frequently used drugs in urinary urgency

Antispasmodic: Oxybutynin 2.5-5 mg/6-10 h Tolterodin 2 mg/12 h Trospum chloride 20 mg/12 h
Tricyclic antidepressants: Amitriptyline 25-50 mg at night Imipramine 25-50 mg at night
NSAID and corticosteroids
Local anaesthetics with or without opioids intravesical route: 2% Lidocaine instillation via catheter, for 20 minutes -1 h 0.5% Bupivacaine combined with morphine 10-20 mg three times a day via catheter, 30 minutes
Anticholinergics via SC route in bolus or in continuous infusion: Hyoscine butylscopolamine 60-120 mg in 24 h

Summary of evidence

4	There is no evidence about the treatment of urinary urgency in PC (282).

Recommendations

D	Due to the lack of evidence about what is the best treatment for urinary urgency in PC, anticholinergic, antispasmodic drugs, NSAID, corticosteroids and local anaesthetics can be used.

6.9. Urgencies

The questions that are going to be answered are:

- What is the most suitable treatment for hypercalcaemia in people in EOL?
- What is the most suitable treatment for spinal cord compression in people in EOL?
- What is the most suitable treatment for seizures in people in EOL?
- What is the most suitable treatment for bleeding in people in EOL?

6.9.1. Hypercalcaemia

Hypercalcaemia occurs in 10-20% of patients with cancer, both in solid tumours and in leukaemia. The cancers that are most commonly associated with hypercalcaemia are breast, lung, prostrate and multiple myeloma (283; 284).

Tumour hypercalcaemia can occur due to three mechanisms: osteolytic metastasis (frequent in breast and lung cancer), tumour hypercalcaemia (tumour protein secretion related to parathyroideal hormone, a frequent cause in non-metastatic tumours and some patients with non-Hodgkin lymphomas) and tumour production of calcitriol (cause of the majority of hypercalcaemias in Hodgkin's disease and in one third of non-Hodgkin lymphomas) (283).

The most characteristic signs and symptoms are described in table 29. Professionals caring for patients in PC must be alert and suspect hypercalcaemia when the general state of patients gets worse without any clear cause and with suggestive symptoms, as there are effective treatments. Treatment is considered necessary when there are symptoms and it may not be necessary if death is considered to be near (284).

Table 29. Clinical Characteristics of malignant hypercalcaemia (284)

General	Gastrointestinal	Neurological	Cardiologic
Dehydration Polydipsia Pruritus	Anorexia Weight loss Nausea Vomiting Constipation Paralytic Ileus	Fatigue Lethargy Confusion Myopathy Seizures Psychosis	Bradycardia Auricular arrhythmias Ventricular arrhythmias Increase in PR interval Decrease of QT interval Broad T wave

The treatment consists in rehydration followed by the administration of hypocalcaemia drugs (bisphosphonates, calcitonin, others). Drugs that produce hypercalcaemia must be withdrawn (thiazide diuretics, vitamins A and B). The seric calcium levels are calculated based on the following formula (284):

Corrected calcium = measured calcium + [40-seric albumin (g/l) x 0,22]

When the corrected calcium figures are over 2.6 mmol/litre (10.4 mg/dl) it is considered hypercalcaemia. The symptoms are generally expressed only as from 3.0 mmol/litre (12 mg/dl). Levels of over 4.0 mmol/litre (16 mg/dl)[8] can produce death in a few days if not treated.

Hydration

Expert opinion 4

Hydration is recommended, either by oral route if the clinical situation of the patient permits this, or by intravenous route in more serious cases. Hydration alone rarely helps normalise the calcium levels and it must be monitored to avoid an overload of fluids. The standard accepted therapy is 2-3 l/day, with daily monitoring of electrolytes. There is no evidence that loop diuretics are useful as a therapy together with hydration and they may worsen the hypovolemia and electrolytic disorders, so their routine use is not recommended (283; 284); they would only be indicated in case of overload.

[8] Conversion to mg/dl: divide between 0.2495.

Bisphosphonates

Bisphosphonates are considered the pharmacological treatment of choice in malignant hypercalcaemia (284; 285).

SR of RCT 1+

One systematic review (132) analysed the efficiency of bisphosphonates on bone morbility in metastatic cancer, also including the effect on hypercalcaemia. Apart from the benefits at bone level (reduction of fractures and need for radiation therapy), the bisphosphonates reduced the risk of hypercalcaemia [OR 0.54 (IC 95%: 0.36-081)].

Another systematic review assessed the efficiency of the different bisphosphonates, doses and series; 26 RCTs were included (285); the search ended in June 2001. The main result was the proportion of patients who reached normocalcaemia. Pamidronate was better than etidronate (7.5 mg/kg) and at low doses of clodronate (600 mg). Pamidronate proved to be similarly efficient at 1500 mg clodronate. Alendronate was equally efficient as 600 mg clodronate and more efficient than etidronate. Zoledronic acid was superior to pamidronate. Ibandronate and pamidronate proved to have similar efficiency, although the studies presented methodological problems. The studies that compared different doses showed that efficiency increases with the dose. The average time required to reach normocalcaemia varied between 2-6 days, and no differences were observed between the different bisphosphonates or doses. The relapse time was less with pamidronate compared with clodronate or etidronate. The review concludes that IV route bisphosphonates are the drugs of choice in acute hypercalcaemia (see table 30), as they achieve normocalcaemia in 70% of the patients and are well tolerated. It recommends the use of high doses of powerful aminobisphosphonates (such as zoledronic, pamidronate), regardless of the basal levels of calcium.

Table 30. Criteria for bisphosphonates in IV infusion for hypercalcaemia (284; 286)

Pamidronate 30-90 mg/2-4 h
Zoledronic 4 mg/15 min
Ibandronic 2-4 mg/1-2 h

Calcitonin

Expert opinion 4

Calcitonin is efficient in approximately one third of the patients and reduces the calcium levels in 4 hours, but normocalcaemia is not generally reached. It is not often used in PC (284). Its efficiency is limited to the first 48 hours (283).

Salmon calcitonin is used by IM or SC route at doses of 4 UI/kg every 12 hours; the doses can increase up to 6-8 UI/kg every 6 hours. Nasal application is not efficient for hypercalcaemia.

Corticosteroids

They are used in haematological tumours or in patients with hypervitaminosis D due to granulomatosis (283; 284). The recommended criterion is 40-100 mg/day prednisolone by oral route (284).

Expert opinion 4

Summary of evidence

4	Hydration is necessary although on its own it is rarely able to normalise the calcium levels, and it must be monitored to avoid fluid overload (283; 284).
1+	Bisphosphonates by IV infusion achieve normocalcaemia in 70% of the patients in 2-6 days and are well tolerated. High doses of powerful aminobisphosphonates seem to be more efficient (285).
4	IM or SC salmon calcitonin is efficient in approximately one third of the patients and reduces the calcium levels in four hours, more quickly than bisphosphonates, but normocalcaemia is rarely reached. Its efficiency is limited to the first 48 hours (283).

Recommendations

√	The possibility of hypercalcaemia must be considered in patients in PC with a worsening of their general state without a clear cause that explains it.
A	The treatment of choice for serious hypercalcaemia is hydration together with hypocalcaemiant drugs.
A	IV bisphosphonates are the drugs of choice for acute hypercalcaemia; high doses of powerful amino-bisphosphonates (such as zoledronic or pamidronic acid).
D	SC or IM salmon calcitonin can be used during the first hours, continuing later with bisphosphonates.
D	Corticosteroids can be used in haematological tumours or in patients with hypervitaminosis D due to granulomatosis.

6.9.2. Spinal cord compression

It is estimated that malignant spinal cord compression (MSCC) could affect 3 to 5% of patients with cancer and that 10% of patients with bone metastasis can develop it (287). The tendency to produce bone metastasis and MSCC depends on the type of tumour. The most frequent is the myeloma followed by prostate, breast and lung cancer. The most frequent location is in the chest (7%), lumbo-sacral (20%) and cervical (10%) areas (287).

MSCC occurs due to the tumour invading the spinal cord channel (external spinal cord compression). It is normal for spinal cord compression to come before the destruction of the cortical bone of the vertebral body. The compression can rarely be internal due to intramedullary metastasis.

Average survival after diagnosing MSCC is six months (288). MSCC is considered a medical emergency, so it must be suspected in patients with back pains and weakness in lower limbs. Disorders of the sphincter function and sensitivity appear in more advanced phases (287). Delays in diagnosis are associated with the lack of recognition of initial neurological symptoms (289).

Apart from the type of tumour, walking difficulties, slowing down of tendinous reflexes, the presence of radiological bone fractures, bone metastases, the duration of bone metastases of more than one year and the age, <50 years are independent risk factors of MSCC (290). In patients with prostrate neoplasia, the tumour extension, the extension of the bone metastasis and the duration of the hormone therapy are also associated with a greater risk of MSCC (289).

The treatment prognosis depends on the previous neurological function, above all the motor function (289).

The diagnostic suspicion needs to be confirmed via a magnetic resonance (289).

The objective of the treatment is to alleviate the pain, prevent complications and preserve the neurological function by means of the available techniques, bearing in mind the patient's individual situation, his or her preferences and the life expectation.

The treatments used until now have been corticosteroids, radiation therapy and surgery.

SR of different types of studies 1+/2+/3

The treatment of MSCC has been assessed in two recent reviews. All the treatments were assessed in the first of them, as well as aspects related to the diagnosis and prognosis of MSCC (289). The second review assessed the role of radiation therapy and surgery via a meta-analysis of prospective and retrospective studies with no control group (291).

RCT 1+

Finally, a non-masked RCT (292), mentioned in one of the reviews (289), compares the combination of surgery with radiation therapy with just radiation therapy.

R of different types of studies 1+/2+

The Loblaw review included two RCTs, one trial in phase II and control case studies on the use of corticosteroids. Dexamethasone, combined with radiation therapy, used in initial bolus of 100 mg proved more effective than lower doses, but it presented a significant increase of serious side effects.

The result variable chosen to assess the response to the treatment was the patients' ability to walk on their own following the treatment. Radiation therapy obtained a response rate of 65%; surgery, 85% (291).

Surgery presented a mortality rate of up to 13% in the following month and up to 54% in patients who presented morbility related to surgery.

RCT 1+

One RCT (292) compared the efficiency of surgery followed by radiation therapy with isolated radiation therapy in 101 patients with confirmed MSCC, in one single vertebral area and with the presence of at least one neurological sign. Both groups also received corticosteroids. The following exclusion criteria were applied: some radiosensitive tumours (leukaemia, lymphomas, myelomas), paraparesia, brain metastasis, MSCC or prior radiation therapy, and expected survival of less than three months.

Survival was greater in the surgical group, with a greater walking ability, 84% compared with 57%, [NNT of 4 (IC 95%: 3 to 11)] and for more time, with less need for corticosteroids and opioids.

Surgical treatment requires a careful selection of patients. Depending on the characteristics of the patients and how the MSCC is present, some authors have prepared criteria that must be considered when making a decision about the most advisable treatment (287) (see table 31).

Table 31. Criteria for the choice of radiation therapy or surgery in MSCC

Surgery	Radiation therapy
• Spinal cord compression due to metastasis of unknown origin • Persistence of symptoms despite radiation therapy • Tumour resistant to radiation therapy • Backbone instability • Cervical compression • Metastasis in one single area	• Radiosensitive tumour • Metastatic lesion at multiple levels • Contraindication of surgery • Patient's choice

Summary of evidence

2+	Corticosteroids, high doses of dexamethasone (100 mg IV in bolus), associated with radiation therapy, increase the treatment response rate (289).
2+	In selected patients, radiation therapy and surgery obtain response rates of 64% and 85%, respectively (291).
1+	Surgery combined with radiation therapy improves survival, the ability to walk and walking time (292) compared with radiation therapy alone.

Recommendations

D	If MSCC is suspected, an NMR must be requested to confirm the diagnosis.
√	The suspicion of MSCC requires the patient to urgently be referred to perform an appropriate study and treatment.
D	An individual evaluation must be carried out on patients with SCC, including level and number of spinal compressions, type of tumour and extension, vital and functional prognosis, degree of neurological affection, patient's preferences and availability of treatment with radiation therapy and surgery.
C	The treatment must be carried out as soon as possible.
B	High doses of corticosteroids are recommended, both in treatments with radiation therapy and with surgery.
D	Radiation therapy as the only treatment is preferable in the case of contraindication of surgery, radiosensitive tumours, established paraplegia, compression at several levels, surgery failure or patient's wishes.
B	Surgery combined with radiation therapy is the treatment of choice in selected patients with a vital prognosis of more than 3 months.

6.9.3. Seizures

A *convulsion* is an episode of generalised involuntary muscular contractions. The epileptic status is defined as a crisis that lasts for more than 30 minutes or the succession of two or more crises without recovering consciousness altogether. However, a crisis that lasts more than 5 minutes must be treated actively (293; 294).

Seizures are not infrequent in PC, above all in patients with brain neoplasias, as in one third of these patient this is the first symptom that leads to the diagnosis and half of them suffer from them throughout their illness (295).

Seizures may also be due to non-oncological diseases subject to care in PC: infections, AIDS, cerebrovascular complications, paraneoplastic disorders, metabolic disorders or toxic effects of drugs (295).

They may also be due to different factors in cancer patients:

- Primary brain tumours and brain metastases (although these cause convulsions less frequently than primary brain tumours) especially from lung cancer and melanoma.
- Chemotherapy: especially if the doses are high or there is hepatic or renal failure, this being one of the limiting factors of the chemotherapy dose.
- Metabolic disorders, often induced by drugs (cyclophosphamide-induced hyponatremia, bisphosphonate-induced hypocalcaemia, cisplatin-induced hypomagnesaemia).
- Paraneoplastic syndromes.
- Cerebrovascular complications (venous sinus thrombosis, brain haemorrhages).
- DCS infection (herpetic above all).
- Cranial radiation therapy (acute encephalopathy by radiation and deferred necrosis) (296).

There is very little existing evidence respect to the diagnosis and treatment of seizures in patients submitted to PC, so they must be extrapolated from the general population or from patients with brain tumours (295).

The first step in the diagnosis of a convulsion is to recognise it as such. It must be distinguished from other types of episodic involuntary muscular contractions such as myoclonus (e.g. opioid-induced), hyperkinesias (e.g. haloperidol or orthopramide-induced) or movement patterns related to a terminal rise of the intracranial pressure (295).

It is essential, therefore, to obtain a detailed description of the episode. This step is taken practically at the same time as the decision about the treatment.

Expert opinion 4

The aetiological diagnosis following a crisis requires an anamnesis, physical examination and additional examinations (analytics, EEG, image studies) which must be done individually in agreement with the state of the patient and his or her preferences.

The treatment of seizures in a palliative patient is the same as in any other patient. In most cases, an epileptic crisis is solved spontaneously in seconds or minutes. However, if it lasts for longer, it will require urgent attention.

If seizures has just started, the aim is to reduce the possibility of lesions to a minimum. So the patient's family and friends must be education in what to do.

Expert opinion 4

If seizures last for more than five minutes or occur one after the other without recovering consciousness during that time, we are facing an epileptic status: a medical emergency. Depending on the clinical situation of the patient, IV diazepam may be used in the first place (297). IM route must not be used due to its irregular absorption. Diazepam also permits rectal administration. In this case, the recommendation is for a person close to the patient to administer 5 to 10 mg of diazepam via this route (298;299). Midazolam is an alternative and has the advantage of being administered by subcutaneous route. In the case of convulsions in the agony phase, these two options (rectal diazepam and subcutaneous midazolam) are especially useful (300).

If seizures persist, the patient must be referred urgently to hospital.

SR of RCT 1+

Preventive treatment with anticonvulsants is not recommended in patients with brain tumour who have still not suffered any crisis (301).

Prophylaxis is indicated in the case of repetition seizures due to primary or metastatic brain neoplasias. This must be carried out, if possible, with one single drug to avoid adverse effects (asthenia, drowsiness and cognitive alterations) (296).

Expert opinion 4

The drugs must chosen individually, bearing in mind the type of crisis, the side effects and possible interactions with other treatments (chemotherapy, corticosteroids, etc.). The use of corticosteroids may mean that the blood levels of many antiepileptic agents have to be monitored (302).

The most commonly used antiepileptic agents in anticonvulsant secondary prophylaxis are presented in appendix 5.

Summary of evidence

1+/4	Rectal route or intravenous diazepam and subcutaneous midazolam are efficient in seizures (298-301).
1+	Anticonvulsant prophylaxis is not efficient in the primary prevention of seizures in patients with brain neoplasias (301).

Recommendations

D	The initial management of a patient with seizures in PC must include the identification and treatment of the possible triggering causes and instructions to the patient's carers, including the possibility of administering anticonvulsant medication.
D	Epileptic status is a medical urgency that requires urgent referral to hospital.

D	The initial treatment of seizures is IV or rectal diazepam. The alternative option is subcutaneous midazolam.
D	If treatment is required to prevent new crises, the treatment must be chosen at an individual level, bearing in mind the types of crisis; the experience of use; the side effects and the possibility of pharmacological interactions, including chemotherapy.

6.9.4. Haemorrhage

Expert opinion 4

6% to 10% of patients with advanced cancer have clinically significant bleeding episodes, which can be expressed in different ways: haemathemesis, melene, haemoptysis, haematuria, epistaxis, vaginal bleeding or bleeding skin ulcer, among others. Any kind of visible and persistent bleeding can be distressing for the patient, family and healthcare team caring for them. It is important to identify patients with a high haemorrhagic risk (see table 32), especially those with a possibility of suffering massive bleeding, such as patients with head and neck cancer and those who have a bad functional situation or bad prior prognosis (303-305).

Table 32. Patients with haemorrhagic risk

- Serious thrombocytopenia
- Extensive head and neck carcinoma
- Extensive, centrally located, lung carcinoma
- Acute or refractory chronic leukaemia
- Myelodysplasia
- Serious hepatopathy
- Myeloproliferative syndrome
- Lung cancer
- Relapsed rectum cancer
- Hepatocarcinoma
- Metastatic tumours (choriocarcinoma, melanoma, renal cell carcinoma)
- Patients with advanced cancer who take oral anticoagulants
- Patients with bone marrow transplant and graft versus host disease
- Treatment with high radiation therapy doses
- Disseminated intravascular coagulation
- Hepatic metastasis

The haemorrhage may be due to a local anatomical cause, such as vascular damage caused by tumour invasion, or it may be the consequence of a systemic process, such as infiltration of the bone marrow, the action of certain drugs or hepatic failure (303; 305) (see table 33).

Table 33. Physiopathology of bleeding in cancer patients

Anatomical factors
Local tumour invasion
Systemic factors
Tumour infiltration of bone marrow (haematological neoplasias) Suppression of bone marrow (chemotherapy and radiation therapy) Disseminated intravascular coagulation Hepatic failure Medication (anticoagulants, NSAID, etc.) Concomitant diseases (hepatic cirrhosis, Von Willebrand disease, etc.)

The episodes must be treated individually, depending on different factors such as the possibility of reversion or control of the cause of the bleedings, the existence of earlier episodes and the response to the treatment received, the current clinical situation and the patient's life prognosis, as well as his or her values and preferences (304)

No intervention studies have been identified on this problem, so recommendations are based on individual clinical preferences and available resources (303-305).

The general and specific therapeutic measures are shown in table 34. Some of them require referring the patient to specialised care (303-305).

The team drafting the CPG proposes a series of applicable measures in those cases when the patient is cared for at home.

Table 34. Treatment of bledding in palliative care

General measures
Identify patients with haemorrhage risk Maintain good communication with patients and their care providers Establish support measures in case of massive bleeding
Specific measures
Local
Compression bandages Plugging (nasal) Haemostatic agents Vasoconstrictor agents (epinephrine, prostaglandins, others)
Special Techniques
Radiation therapy Surgery (ligature of blood vessels) Endoscopic operations Interventionist radiology (embolisation)
Systemic
Vitamin K Antifibrinolytic agents (tranexamic acid, aminocaproic acid) Somatostatin analogues (octreotide) Platelet transfusions and other blood products

Summary of evidence

4	There are no intervention studies on applicable measures in patients with bledding in EOL, so the recommendations made are based on narrative reviews and consensus (303-305).

Recommendations

D	The patient's carers must be warned and prepared for the risk of the possibility of massive bleeding.
D	The availability of urgent care must be offered with the longest time coverage possible, including a direct telephone contact for the case of massive bleeding.
D	The preparation of a plan of action is recommended for risk patients, with instructions for carers, including the following: a) Place a bowl and dark-coloured towels at the patient's head to compress the point of haemorrhage and absorb and dissimulate the blood. b) Place the patient on his or her side in case of haematemesis or haemoptysis to prevent choking. c) Prepare a syringe preloaded with midazolam to carry out emergency sedation with 5-10 mg administered parenterally, preferably subcutaneously – the process will be made easier if a syringe driver has been previously inserted-, which could be repeated if necessary.

7. Psychosocial and spiritual support to the person in EOL

The questions that are going to be answered are:

- How to identify the psychosocial needs of people in EOL?
- How best to attend to the psychosocial needs?
- How are the spiritual needs identified?
- How do the spiritual needs influence the evolution of people in EOL?
- What is the most suitable strategy to attend to the spiritual needs of people in EOL?

7.1. Psychosocial support

7.1.1. Psychosocial needs

Coping with a life-threatening illness gives rise to a series of psychosocial needs in patients –apart from psychiatric disorders-, such as anxiety, depression, abuse of substances, etc. People use different resources to respond to the psychological suffering, which include their own coping sources and the emotional support of family and friends. However, the level and nature of the suffering is such at times that professional support may be beneficial (12).

The Block review (306) deals with this topic, although it specifies that there is not a lot of research in EOL and that the conclusions are often derived from patients with cancer, HIV-AIDS, or older people.

SR of different types of studies 1+/2+/3/Q

They recommend an assessment of the psychosocial aspects that considers the following fields:

- **Aspects relating to the moment in life**

Response to the illness will change according to the moment of life and the circumstances. Considerations such as if the patient has young children, if future expectations are shattered before time, etc. must be taken into account.

- **Meaning and impact of the illness**

Every illness has a special meaning for each patient (cancer, cardiopathy, HIV-AIDS).

Finding a meaning for life at that time is negatively correlated to depression and associated with the ability to tolerate symptoms and with the satisfaction with one's own quality of life.

- **Coping style**

Comprised of strategies that are used to solve problems. This includes denial, avoidance, fighting spirit, etc. It can often be found that one same patient uses several strategies: coping with what they feel able to assume and avoiding what overwhelms them. Extreme denial is a symptom of depression.

- **Impact on the perception of self**

There are many constructs for the term, dignity, from independence and decision-capacity to maintaining one's body image, hygiene or continuity in relationships.

- **Relationships**

Concern for family members is usually an essential aspect in patients in EOL. According to a study mentioned in the review, from 92 to 97% consider this aspect to be important or very important.

- **Sources of stress**

These can be economic, work, legal, etc.

- **Spiritual resources**

- **Economic circumstances**

The illness can have a very great economic impact on the patient and his/her family.

- **Physician-patient relationship**

The patient must feel secure, knowing that his or her needs are being cared for.

7.1.2. Psychosocial interventions

SR of different types of studies 1+/2+

There are different systematic reviews about the effectiveness of psychotherapy, most of them performed on cancer patients. The Newell systematic review (307), performed on patients with different stages of cancer, included 150 studies. Unlike other earlier SRs, he carried out an exhaustive evaluation of the quality of the individual studies and described the results in agreement with the objective of the therapy (global effect, stress or suffering, functionality and quality of life, coping, etc.) and on the type of therapy. It did have limitations such as the low quality of the studies and the fact that these were in English. Of the interventions studied, group therapy, education, structured or non-structured counselling and cognitive, behavioural therapy seem to be the interventions that offer the most consistent results in the medium and long term. The benefits observed are based mainly on psychosocial aspects (results such as adaptation to the new situation, depression, anxiety, etc.). Different patients with different kinds or stages of illness may have different needs. There is evidence that individualised interventions such as those provided by specialised nursing staff or by a multi-disciplinary team, are efficient. The benefit of psychotherapy over physical aspects or on survival is more uncertain.

SR of RCT 1+

Later, the Uitterhoeve review (308) evaluated 10 clinical trials that included 13 interventions with different content; the majority used behavioural techniques (relaxation, etc.), support groups, psychological advice or combinations of several interventions, in patients with advanced cancer. Most of the interventions were performed by psychotherapist psychologists or specifically trained nursing staff. All the studies came from the Anglo-Saxon setting. The heterogeneity did not permit a meta-analysis. Three of the studies were on patients in a clearly advanced phase, two of them with lung cancer.

According to the general results of the review, the major benefit is observed in the reduction of sadness and depression, and an improvement is also observed in the coping mechanisms. It is not explained which type of intervention is more efficient, or who is the ideal professional to carry it out or if an individual or group type intervention is better.

SR of different types of studies 1+/2+/3/Q

Although the articles mentioned refer to psychosocial interventions, they focus more on psychological aspects. One SR (309) sought studies on how the information concerning older people was communicated between health services (mainly nursing staff) and social services. The results show a lack of evidence in this area. The information mechanisms were inadequate (producing delay and dissatisfaction between patients and professionals) and were based mainly on informal communication between professionals. The most adequate strategy was the communication of information through *key workers*, who provide a point of contact between the hospital and community levels, although this option is not free from problems, either. The lack of common objectives among the different professionals of the different care fields or the mutual lack of knowledge of the professional roles, are some of them.

The NICE guideline makes the following recommendations in this field (12):

- The patient's psychological wellbeing must be evaluated.
- All professionals responsible for the patient's care must offer basic emotional support.

- If necessary, patient must be referred to specialised care.
- The personnel must receive training and supervision.

The Australian guidelines for psychosocial aspects in adults with cancer offers the following conclusions:

- Education sessions can improve adjustment and knowledge, and increase positive self-concept.
- Psychological interventions are associated with improvements in quality of life, mood, coping, sense of personal control and physical and functional adjustment..
- Open communication and expression of feelings promotes adjustment

One of the aspects associated with a good death is the patient's social life in EOL.

In short, we can say that it is necessary to make an evaluation that contemplates the different psychosocial aspects and it seems that the behavioural and advisory interventions can improve the quality of life, the coping capacity and depression; but there is less data to specify which type of intervention is more efficient. The interventions involve the need for professionals with adequate preparation to carry them out.

Summary of evidence

3	The psychosocial evaluation of patients in PC includes the following fields: aspects relating to the moment in life, meaning and impact of the illness, coping style, impact on the perception of self, relationships, sources of stress, spiritual resources, economic circumstances, physician-patient relationship (306).
1+	In patients with advanced cancer, psychosocial interventions produce beneficial effects, such as the reduction of sadness and depression, and improve the coping mechanisms (308).
1+/2+	In patients with cancer at different stages of evolution, psychotherapy basically improves psychosocial aspects such as the adjustment to the new situation, depression, anxiety, etc. The benefit over physical aspects or over survival is more uncertain. With respect to the interventions studied, group therapy, education, structured or non-structured counselling and cognitive-behavioural therapy seem to be the ones that offer the most consistent results in the medium and long term. Individualised interventions, such as those provided by specialised nursing staff or by a multidisciplinary team are efficient. Different patients with different kinds or stages of the illness can have different needs (307).
1+	There is less data to specify which type of intervention is more efficient, how long they should last and how intense they should be, or who is the most appropriate professional to carry it out (307; 308).
1+/2+/3/Q	The information transfer mechanisms between health and social workers are inadequate. The most efficient method could be *key informers*. The evidence about the most appropriate professional profile and setting (hospital or community) is inadequate (309).

Recommendations

B	The psychosocial wellbeing of patients with life-threatening diseases must be evaluated on a regular basis.
D	The psychosocial assessment of the patient in PC should include the following fields: aspects related to the moment in life, meaning and impact of the disease, coping style, impact on the perception of self, relations (type of family, friends, etc.), sources of stress (economic difficulties, family problems, etc.), spiritual resources, economic circumstances, doctor-patient relationship, social resources network (socio-health centres, social workers, etc.).
B	Health professionals who care for patients in PC should offer them basic emotional support.
D	Patients with significant levels of psychological suffering should be referred to receive specialised psychological support.
D	The training of health professionals in psychosocial support techniques should be promoted.
C	Increasing awareness and establishing common objectives are the first step to build bridges between health and social workers of hospital and community fields.

7.2. Spiritual support

7.2.1. Introduction

All PC guidelines mention spirituality as an important aspect to be considered in patients in EOL: It is also present in the actual definition of PC. Spirituality is a topic that has some peculiarities that make it impossible to address in the same way as other more specific aspects, such as managing symptoms.

Firstly, a definition of what we understand by *spirituality* must be given and also how it differs from other psychological aspects.

The Block systematic review (306) focuses on psychological aspects of care in EOL, such as the different coping styles, the sources of stress, personal relationships, etc. Some authors (306) talk about *psychospiritual wellbeing* and define this as a subjective experience that incorporates emotional health and concerns about the meaning of life; but as other authors point out, whether the health professionals believe or not if there is a difference between body, mind and spirit this has no influence on offering good PC focused on the patient. The needs called spiritual needs can be deduced from the behaviours or be stated specifically by the patient. They can be distinguished from aspects such as moods or economic problems, personal relationships, etc.

In agreement with the definition of *spirituality* used by Holloway (310), it is «a dimension that combines attitude, beliefs, feelings and practices that go much deeper than what is strictly rational and material ».

Based on this idea of spirituality –not necessarily linked to religion-, the appraisal of this need in any patient must be considered essential.

7.2.2. Appraisal of spiritual needs

Expert opinion 4

Different instruments have been developed for this purpose, such as scales or questionnaires like the System of Belief Inventory (SBI) (10), or the RCOPE (311). The ICSI guideline (11) for PC proposes an acronym, SPIRIT, to recognise spiritual needs, which must include: system of spiritual beliefs, personal spirituality, integration in a spiritual community, rituals, restrictions, implications for the medical care and planning of last provisions.

Bayés and Borrás advise establishing a simple screening instrument and bearing in mind that patients prefer to talk rather than fill in questionnaires (312). The ideal instrument are basic communication techniques: open-ended questions, active listening, silences and physical contact.

Some authors have proposed four questions that teams caring for patients in PC could ask to explore spiritual needs in this context (313):

— What is your faith or what are your beliefs?

— What role do they play in caring for your health?

— Do you form part of a spiritual or religious group?

— How could these questions be managed by the team caring for the patient?

In any case, there is no unanimous belief about the advisability of using instruments and less so about which instrument would be the most appropriate.

It is important to consider the cultural differences with respect to spirituality. In this article, Holloway (310) tries to find a transcultural framework that enables health professionals to work in PC regardless of the cultural context. He establishes a typology of ways of understanding death (as a light, as a mystery, as darkness, etc.) which in the end can be summed up in three groups: positive, negative and dialectic vision. He concludes that there is a lot more in common with respect to death than what separates us, and that the differences do not justify the lack of attention to these aspects in people who belong to different cultural groups to our own.

7.2.3. Influence of spiritual aspects on patients' evolution

SR of different types of studies 2+/3

The Puchalski review (314) only considered five American PC magazines between 1994 and 1998 and concluded that more research is necessary and that there are no spiritual or best care standards in this field.

The Lin and Bauer review (315) studied the role of the psycho-spiritual state in patients with advanced cancer, evaluating quasi-experimental and descriptive studies (both quantitative and qualitative). Its main findings include:

Sense of faith

All the studies talk about faith referring to its religious aspect, showing that faith provides strength, it is associated with positive attitudes in connection with the diagnosis and quality of life and acts as support to individuals with terminal cancer.

Empowerment and confidence

This section includes an absence of economic problems, sense of independence and control, joy and interior peace, will to live and fulfilment of the life project. These aspects are related to an increase of psycho-social wellbeing, a life with meaning, with quality of life and with a good death.

Living with meaning and hope

Patients who are able to find a meaning to life and have hope have greater psycho-spiritual wellbeing, better quality of life and less psychological suffering.

Several factors contribute to this: good personal relationships and capacity to maintain a sense of normality in daily life.

The authors conclude that these aspects appear repeatedly in different studies, but they highlight the need for further research into this field. Most of the research studies have been conducted on white American population, and other cultures may produce differences (315).

SR of different types of studies 2+

There are no studies that have been appropriately designed to measure the impact of any specifically designed intervention on spiritual suffering, but where the literature consulted coincides is on the importance of bearing this dimension of the human being in mind and its repercussions on the general wellbeing of the individual in EOL (1; 10; 11; 12; 310; 315; 316).

CPG and Expert opinion 4

There is no appropriate evidence, either, that determines how spiritual care should be provided. The NICE guideline (12) recommends listening to the patient's experiences and the questions that may occur to him or her; affirming their humanity; protecting their dignity, self-esteem and identity; and guaranteeing the offer of spiritual support as an integral part of care that covers psychological, spiritual, social and emotional care, in agreement with the patient's beliefs and his or her life philosophy. It adds that it is possible to offer many aspects of spiritual support in any context; by family, friends, faith groups, priests and other spiritual advisors and health professionals. The patients' spiritual needs can vary throughout time.

Summary of evidence

4	*Spirituality* is understood as a dimension that combines attitudes, beliefs, feelings and practices that go deeper than what is strictly rational and material, a much broader conception than the religious one (310).
3	Spirituality has an impact on the general wellbeing of patients in PC and on their quality of life (315).
3	There is no unanimity respect to the advisability of using a structured instrument or scale to appraise the spiritual needs, and even less so about which would be the best (12; 311; 312).
3	There is no appropriate evidence that determines which is the best way of providing spiritual support. Failing this, the guidelines and literature consulted underline the importance of bearing this dimension in mind (12).

Recommendations

D	The team caring for a person in PC should bear in mind his or her spiritual beliefs and needs.
D	Failing appropriate evidence on how to best provide spiritual support, it is recommended to offer this support as an integral part of the care, whatever the health-care context, and with the approach based on effective communication principles.
D	It is important to consider the cultural differences with respect to spirituality. This must not justify a lack of attention to these aspects in people who belong to different cultural groups to our own.

8. Psychosocial support to the family

The questions that are going to be answered are:

- How are the family's psychosocial support needs identified?
- What is the best way of attending to the family's support and psychosocial needs?
- What are the risk factors of family exhaustion syndrome?

8.1. Family's psychosocial support needs

SR of different types of studies 1+/2+/3/Q

According to the Harding SR (317), there is a lot of information about the needs of the carers of patients who receive home care for cancer and PC, but little information about the effectiveness of the interventions. According to the studies, the needs are: home help, informal help, information, economic help and help for tiredness, anxiety and isolation. The priority matters for carers are information and psychological support.

SR of different types of studies 2+/Q

Another review provides information about this topic (316), although not referring to patients in PC, but to carers of older people. The studies included in this review are mainly on patients with dementia, where the distinction between chronic and terminal is not so clear.

The needs and desires expressed by carers of older patients are:

- They want to satisfy their training needs in groups of carer
- They want respite care services
- They experience negative emotions such as burden, stress and concern when they look after an older person at home
- They would like a support group network to exist
- They fear social isolation
- They fear loss of control, changes of role in the relationships and loss of reciprocity

Qualitative study Q

In the bibliographic sources studied, the concept of burden varies a great deal between individuals and circumstances. As mentioned in the introduction, it was considered appropriate to include the vision of carers in this CPG, through a qualitative study. The work analysis provides key points that have to do with the family's support needs. Many carers find a meaning in looking after a relation in EOL, they consider it acceptable to assume most of the responsibility and work, and even find a motive of pride, support and reinforcement that helps them in the bereavement process. It is important, therefore, to find an equilibrium between the help that they may sometimes need and what they are willing to delegate on others; what can lead them to give up certain support measures such as breathing space services, income, etc.

One repeated request is for support and company. Carers often express their feelings of abandonment and loneliness related to the lack of support in all spheres.

Another aspect they mention is the lack of quality in the services, understood as access difficulties, excess red tape, lack of coordination between levels and gaps in the healthcare, which make them fear, for example, the problems that might arise at weekends.

Finally, with respect to their role in decision-making, carers express they are in favour of guided and accompanied participation, halfway between the former paternalistic attitudes and the current tendency that they consider as a relinquishment of responsibilities by the professionals: leaving decisions, for which they do not feel prepared, in the hands of the family.

8.2. Perception of burden in carers

A study with 96 carers of cancer patients who receive home PC concludes that the determining factor for experiencing the care as a burden is the carer's depression. Other aspects have a more indirect influence such as anxiety and the state of health of the carer, which have an affect on the appearance of depression, not directly on the perception of burden (316).

Case series 3

A qualitative study that includes information from in-depth interviews with 13 carers, establishes vulnerability as an essential category.

Qualitative studies Q

Factors that predispose to this vulnerability would be: the care burden, the reduction of the carer's own activities, fear, lack of security, solitude, coping with death and lack of support.

Protection factors include: continuation of former activities, hope (referring to realistic hope, not to miracles), the feeling of keeping control, the satisfaction (the care offered) and the instrumental or emotional support (316).

8.3. Care of family's psychosocial and support needs

The Harding review (317) found 22 articles, 9 of them specific on carers. 6 of them were finally evaluated.

SR of different types of studies 1+/2+/3/Q

The studies centre more on describing the interventions than on appraising their results. The kinds of interventions described are: home care, breathing space services, social networks and activities, individual and group interventions. It is impossible to conclude which intervention format is the best, for how long or to what extent the cultural differences have an influence on the results. Maybe the RCTs are not the ideal design for this type of interventions.

- Home care (general nursing service) provides satisfaction to the carers, but does not cover all their needs. **2+**

- Respite care services cause ambivalent feelings in the carers, although they are perceived by them as important. **3**
- Activities and social networks for carers have positive effects on them. **1+**
- Individual interventions have uncertain efficiency. They are high-cost and little used services. In a study they only proved to be efficient in the subgroup of carers with a higher degree of suffering. **2+**
- Group interventions may not be appropriate for all carers, such as the psychologically more vulnerable groups. They are not often used and are acceptable for carers with specific demographic profiles. They can improve knowledge, coping and satisfaction. **Several**

The Harding review (317) evaluates the evidence of seven interventions and concludes that, more than seeking spectacular changes, the aim is to identify the useful elements of such interventions. The objectives must be established by the carer and not by the professional. The review underlines that no single model is going to be acceptable for all carers or is going to cover all the needs.

The review on the care of older people (316) concludes that there is moderate evidence about education programmes for carers and insufficient evidence about the respite care services and about the ethnic influences on the perception of the role of carer. **SR from different kinds of studies 1+/2+/3/Q**

The NICE guideline formulates the following recommendations: **GPC Expert opinion 4**

- Offer carers the possibility of expressing their support and information needs, regardless of the patient's needs, bearing in mind ethnic or cultural preferences.
- Incorporate carers into interviews about treatment and care whenever possible, always in agreement with the patient.
- Offer carers and families access to existing advice, support and information sources.

Summary of evidence

3	Carers' needs include: home help, support, information, economic aid and help for tiredness, anxiety and isolation. The priority matters for the carers are information and psychological support (317).
2+	There is a lot of evidence about the carers' needs that are not covered, but little about the effectiveness of the interventions to cover them. No single model is going to be acceptable for all carers nor is it going to cover all the needs (317).
1+/2+/3/Q	Home care provides satisfaction for carers. Repite care services provoke ambivalent feelings in the carers and their acceptability is variable. Activities and social networks for carers have positive effects on them. Individual interventions have uncertain efficiency, they are not often used and have a high cost. Group interventions are not appropriate for all carers, they are not often used and have variable acceptability (317).

3/Q	According to different studies, depression or the vulnerability of the carer are determining factors to experience care as a burden. Predisposing factors to this vulnerability are the care load, reduction of the carer's own activities, fear, lack of security, solitude, coping with death and lack of support (316).

Recommendations

C	Carers must be offered the possibility of expressing their needs for support and information.
D	It is recommended to offer basic emotional support to carers.
C	The service planning for the carers should include the following premises: a) The services must be focused on the carers' needs. b) The accessibility and acceptability must be evaluated at the onset. c) The objectives must be clear and modest. d) The results should be assessed.
D	It is advisable to offer the most vulnerable or depressed carers intensive psycho-social support or specialised services.

9. Care during the last days. Agony

The questions that are going to be answered are:

- What kind of care must be given to patients and their families during the last days of life?
- What is the most suitable treatment for the death rattle of the dying person?

9.1. Introduction

The last days of the patient's life, *terminal phase*, require special care. New needs and causes of suffering both for the patient and for the family can appear in this stage. These needs require an approach aimed at fostering spiritual, emotional and physical comfort and wellbeing; at fostering an dignified death and in peace; and at supporting families and carers so that the memory of this phase is as positive as possible (318).

Suffering that is not sufficiently alleviated during the days prior to the death of the patient is always remembered by families and may cause great suffering for months and even years, and at times it makes them forget the care of previous stages.

Care over the last days of the patient implies an adequate diagnosis, understanding the characteristics of the patient's suffering, providing the best care and supporting the family and close friends (318).

9.2. Diagnosis, signs and symptoms in the dying person's terminal phase

The first challenge that arises in this phase is its acknowledgement, as well as the comprehension of the multifactoral nature of suffering.

Some of the characteristics that identify the person during this final phase include:

- Increase of the feeling of tiredness, weakness and drowsiness
- Less interest in getting out of bed or receiving visits
- Less interest in what is happening around them
- More frequent confusion, occasionally accompanied by anxiety and unease.

Some of these aspects may not be new; but it is important, and also difficult, to know if the patient is in a terminal phase or it is a new relapse with remission such as may have occurred in the past, due to the implications involved (1).

According to a prospective study conducted in oncology services, general hospitals, homecare teams and specialised centres in PC of Catalonia (319), the most frequent symptoms are anorexia, asthenia, dry mouth, confusion, constipation, dyspnoea, dysphagia and anxiety.

Carers and physicians may evaluate the symptoms of the last days of life in a different way to the patient. In a study conducted at a hospice (320), the symptoms that produced greatest discomfort in patients during the last week of life were asthenia, cachexia and anorexia, with little agreement with the evaluation of carers and physicians. The patients and physicians only agreed with respect to for pain, dyspnoea and coughing. Physicians tended to undervalue symptoms that were relevant for patients and were causes of suffering for them.

Descriptive study 3

The clearest signs of a close death can be evaluated by monitoring the patient's state each day (318). In cancer patients, the signs that are often associated with the terminal phase are (321): patient's confinement to bed, semicomatose state, limited intake of liquids or small sips, inability to take drugs orally.

Expert opinion 4

However, the diagnosis of the agony phase is not free from difficulties, especially in non-cancer patients (see table 35), so it is important for members of the team to be in agreement both relating to the prognosis and to the information given to patient and family.

Table 35. Overcoming the barriers for care over the last days or hours (321)

Barriers for diagnosing the terminal phase
1. Hope that the patient may improve.
2. Absence of a definite diagnosis.
3. Agreement to not very realistic or futile operations.
4. Disagreement about the patient's situation.
5. Lack of recognition of the key symptoms and signs.
6. Lack of knowledge of prescription criteria.
7. Communication difficulties with the patient and family.
8. Doubts about withdrawing or maintaining treatments.
9. Fear of shortening life.
10. Doubts about cardiopulmonary resuscitation.
11. Cultural and spiritual barriers.
12. Medical-legal aspects.

Effects on patient and family if the diagnosis is not made
1. The patient and family are not aware that death is imminent.
2. The patient loses trust in the physicians the more they seem to ignore that his or her condition is deteriorating.
3. The patient and family receive contradictory messages from the team.
4. The patient dies without an adequate control of symptoms, which produces suffering and makes an dignified death impossible.
5. The patient and family feel dissatisfied.
6. There is a possibility of the CPR being initiated inappropriately at the time of death.
7. The cultural and spiritual needs are not covered.
8. There is a risk of complications appearing during the bereavement and of formal complaints about the care.
Educational objectives to overcome the barriers to the diagnosis of terminal phase
1. Be sensitive when informing about the death and agony.
2. Work in a multidisciplinary team.
3. Adequately prescribe: suspend inappropriate treatments, transition of oral route to SC, prescribe appropriate drugs for symptoms during agony, use infusion pumps.
4. Recognise the key symptoms and signs in the agony.
5. Describe a coherent ethical framework with the patient, in aspect such as the resuscitation, withdrawal or maintenance of treatments, therapies that can shorten life or futile therapies.
6. Bear in mind cultural and religious traditions and rites.
7. Bear in mind medical and legal aspects.
8. Appropriately refer to specialised teams.

Once the diagnosis has been made, the team can re-orientate the care of the patient and of his or her family (12).

9.3. Care of patients and family during the last days or hours of life

Although it may be difficult for professionals to recognise and accept that the patient has entered this phase, it is essential to be able to attend to the special demands that arise in different fields. (12; 321):

Expert opinion 4

9.3.1. Physical care

- Review the medication and suspend all treatment that is not essential.
- Make sure that any medication that might be necessary is available and prepare alternatives to oral route (subcutaneous or rectal).

- Suspend all unnecessary interventions and tests (analytics, checking vital signs, etc.).
- Maintain observation to obtain the best possible control of symptoms.

9.3.2. Psychological aspects

- Explore the patient's fears and desires.
- Let the patient express his or her sadness and anxiety.
- Calm him or her down with respect to the symptoms, assuring them that they will be offered all the possible means to alleviate the suffering.

9.3.3. Social or family aspects

- Make sure that the family is aware of the patient's state of imminent death.
- Use clear language, without ambiguities; do not take knowledge about the agony for granted.
- Consider all the reasons for doubt and concern that might arise: tiredness, fear of responsibilities, fear of not realising that death is imminent, feelings of blame for moments of distraction or rest.
- Provide a calm quiet place to spend the last days with the patient.

9.3.4. Spiritual aspects

- Be receptive with respect to the patient's and family's cultural and religious needs.
- Provide the patient with access to rites, visits from members of a religious order, etc. if that is what they want

9.3.5. Aspects relating to the environment where the patient is cared for

- Intimacy.
- Hygiene and facilities to go to the bathroom, adapted to the needs of fragile people.
- Calm and silent environment, with no troublesome noises.
- Sufficient space to permit family and friends to sit down comfortably with the patient.

- Amenities so that family can spend the night near the patient, to receive comfort at difficult times and be able to remain outside the room.

Expert opinion 4

The factors that influence decision-making about death (at home, hospital, PC units, etc.) vary depending on the patient's needs, the available resources and the preferences both of the patient and of the family. At times, as a result of the progression of the illness and the increase of needs, both the patient and family may change their minds about the preference of the place to die. During this stage of life, the sick person expresses anxiety as they feel they are a burden for the family and sometimes they ask to be admitted. On the other hand, health organisations should have flexible systems and resources to be able to transfer patients who wish to die at home and do not have the necessary means or conditions (12).

9.3.6. Premortem death rattles

Death rattles of the dying person are a very frequent and specific symptom in this phase. They refer to the noises produced by oscillating movements of the secretions of the upper respiratory tracts during inhalation and exhalation. They generally only occur in patients who are so confused or weakened that they cannot expectorate (322).

The risk factors that are more frequently associated with the dying person's death rattles are lung and brain cancer, whilst the death rattles more refractory to the treatment are associated with cardiopulmonary pathology (including infection, pulmonary oedema and aspiration). According to some authors the more refractory death rattles are known as *pseudodeath rattles* and do not respond well to anticholinergic therapy (322).

Apart from the general measures (semi-prone position to facilitate postural drainage, explain the physiopathological process to family, gentle nasopharyngeal or tracheal suction), the use of antisecretory drugs is recommended, which must be initiated as soon as possible. The most commonly used drug in our setting is butylscopolamine by SC route. Other drugs such as scopolamine bromhydrate or glycopyrrolate can be used, but the latter are not marketed in Spain.

Case series 3

No clinical trials have been located that compare the efficiency of these drugs. The cases series suggest that up to 75% of patients with dying person's death rattles respond to antimuscarininic drugs (322), although the validity of these data is limited.

The normal dose of butylscopolamine is in SC bolus of 20 mg/4-6 h or via infuser, 100 mg/24h. Scopolamine bromhydrate is used at doses of 0.5-1 mg/6 hours.

Summary of evidence

4	Recognition of key symptoms and signs of the patient during the last days or hours of life is a complex process. The clearest signs of a close death can be evaluated by daily monitoring the patient's state (318). In cancer patients, the signs that are frequently associated with the terminal phase are (321): a) Patient's confinement to bed b) Semi-comatose state c) Limited intake of liquids or sips d) Inability to take drugs by oral route
3	The case series suggest that up to 75% of patients with dying person's death rattles respond to antimuscarinic drugs (butylscopolamine, scopolamine bromhydrate) (322).

Recommendations

D	The appropriate care during the last days of life should include: a) Informing the family and carers about the close death situation and, in general, the necessary and appropriate information according to needs. b) Explaining and reaching a consensus about the care plan with the patient and his or her family. c) Evaluating the medication taken by the patient, suspending non-essential drugs after explaining the reasons. d) Treating the symptoms that produce suffering. The necessary drugs must be available if the patient is at home. e) Interrupting interventions or unnecessary or futile tests, according to the patient's desires. f) Evaluating the psychological, religious and spiritual needs of the patient, his or her family and carers. g) Providing care in a calm environment, respecting intimacy and facilitating the proximity of family and friends. h) Providing the ways and necessary resources for hospitalisation and for home-care.
D	Premortem death-rattles should be treated via the use of SC scopolamine butyl bromide.

10. Palliative sedation

The questions that are going to be answered are:

- What are the indications to carry out palliative sedation?
- What must the decision-making process be like in palliative sedation?
- Which drugs and administration routes are recommended for palliative sedation?

10.1. Introduction

The term *sedation* has been used with different meanings. In the bibliographic review, four relevant reviews have been found in connection with the concept of sedation (323-326). Sedation can be *intermittent* (permits alert periods) or *continuous* (permanent reduction of level of consciousness); *superficial* (permits patient's communication, verbal or non-verbal) or *deep* (maintains the patient in state of unconsciousness) (324; 326). The different studies show great variability in the frequency of the refractory symptoms which sedation is used to alleviate.

Within the framework of PC, the objective of sedation is to alleviate the patient's suffering by a proportionate reduction of the level of consciousness. *Palliative sedation* is understood as the deliberate administration of drugs, in the dosage and combinations required to reduce the consciousness of a patient with an advanced or terminal illness, both when necessary to adequately alleviate one or more refractory symptoms and with their explicit consent (326). *Sedation in agony* is a singular case of palliative sedation and it is defined as the deliberate administration of drugs to achieve alleviation of physical or psychological suffering, not attainable by other measures, via the sufficient deep and likely irreversible reduction of the consciousness of a patient whose death is foreseen to be very close (326).

10.2. Palliative sedation process in agony

Expert opinion 4

The palliative sedation process in agony has to satisfy a series of requirements (324):

- Correct therapeutic indication.
- Explicit consent of the patient, or of the family if the patient is incompetent.
- Clear and complete information about the process, with record on the medical history.
- Administration of the necessary doses and combinations of drugs to achieve the appropriate sedation level.

10.2.1. Therapeutic indication

Correct prescription of palliative sedation requires:

- Meticulous assessment of the diagnosis of end-of-life.
- The presence of refractory psychic or physical suffering and symptoms.
- An assessment of the patient's competence in decision-making (324; 326).

End-of-life Diagnosis (terminality)

Apart from the medical prediction, the use of validated instruments to estimate the survival or functional state may be useful, such as the PaP index or the Karnofsky functional scale, as well as the presence of prognostic factors (see chapter 4.4).

Refractory Suffering and Symptoms

Refractory symptom is understood as suffering that cannot be appropriately controlled despite the efforts to find tolerable treatment, which does not compromise consciousness and in a reasonable period of time. A distinction between *avoidable* and *non-avoidable suffering* is crucial to determine on which aspects of avoidable suffering intervention is possible (via symptom control, psychosocial interventions, care of the environment, etc.) (22). When the intervention possibilities run out, it is understood that the suffering is refractory. In the case of uncertainty about the refractory nature of a symptom, consultation with other experts is recommended (324).

It is necessary to make sure that the all the intervention possibilities to control symptoms have been exhausted. This is especially important in the case of pain. Before deciding upon a sedation procedure, correct treatment of the pain must be guaranteed (327).

Assessment of the patient's competence in decision-making

An assessment of the patient's competence is crucial; in other words, his or her capacity to understand the relevant information, express their desires and know the implications of their decision (324). The patient's competence should be appraised by an experienced team. The involvement and coordination with the primary health care physician is a key aspect at this point.

10.2.2. Patient's consent

Consent means that the patient is competent to make decisions and that, adequately informed, expresses his or her explicit desire for sedation.

Expert opinion 4

Competent patient

Verbal consent is considered sufficient (326), although at times it could be given in writing. Record must always be kept in the medical history.

Legislation
LG

Incompetent patient

The Preliminary Instructions and Living Wills Registry must be consulted. If patient has not left a written record of his or her wishes in connection with decisions in end-of-life, the medical team must appraise the patient's wishes with family or friends, considering the previously expressed desires and values (the possibility of the general practitioner having taken note of the patient's desires, during different visits, will be taken into account, and it is recommendable for these to be recorded in the medical history). In this case, the communication process with the family must satisfy the same requirements as necessary to obtain the patient's consent and which have been described when commenting on the evaluation of the patient's competence.

Due to the complexity of making decisions on sedation, when this situation is foreseeable, it is important to work with the patient regarding his or her opinion in this regard in advance and as a preventive measure, before agony arrives.

Therapeutic privilege

If the patient has expressly his or her will not to be informed, his or her best interest will be taken into account, determined by the therapeutic indication and with the express consent of his or her family.

Information to be communicated

The team must determine and individually consider the benefits and possible harm of the information that will be disclosed (324), which will be comprised of the following data:

- Patient's situation: physical situation, incurability, expected survival.
- Suffering (presence of refractory suffering, causes of suffering, treatments that have been tested, reasoning of the sedation decision).
- Objective of the sedation (alleviate suffering).
- Sedation method: medication that reduces the level of consciousness, with option to discontinue sedation.
- Sedation effects: on the level of consciousness, communication, oral intake, possibility of complications..
- Treatment and care after sedation, to maximise comfort.
- Expected results if sedation is not carried out: other options, degree of suffering, expected survival.

Health professionals must carefully consider the preferences of both patient and family, explaining to the family that their role is to estimate the person's desire, that the family is not totally responsible for all the patient's decisions and that the team should share the responsibility of the sedation decision (324).

10.2.3. Information to the therapeutic team

It is advisable for the professionals involved in caring for the patient to have a knowledge of the sedation process (see figure 12).

10.2.4. Drug administration

There is little scientific evidence with respect to which medication and what dosage must be used for palliative sedation (323; 324; 328).

In a review on terminal sedation in palliative medicine 11 non-opioid drugs were described at variable dosages. Midazolam was the most commonly used drug, with efficiency that varied between 75 and 100%. No drug proved to be better than the others (328).

SR of case series 3

The most normally used pharmacological groups for sedation are benzodiazepines (midazolam), neuroleptics (levomepromazine), barbiturates (phenobarbital) and anaesthetics (propofol) (329). Opioids are not recommended as a specific medication for inducing palliative sedation, but they will be used concomitantly if the refractory symptom is pain or dyspnoea and also if the patient was taking them previously (328; 329) (see table 36).

Figure 12. Sedation Process

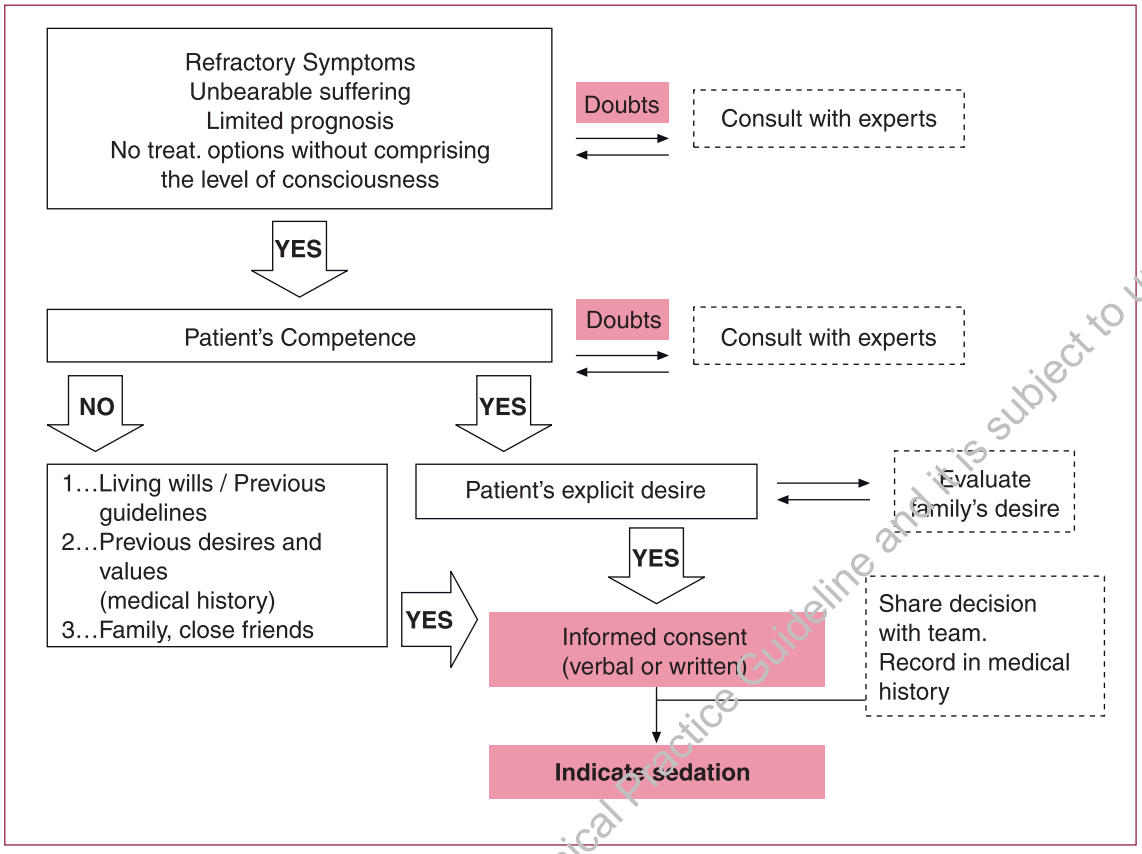


Table 36. Drugs and reference dosage for palliative sedation

Drug	Subcutaneous dosage	Intravenous Dosage
Midazolam* (ampoules 15 mg/3 ml)	Induction (bolus): 2.5-5 mg** Initial SCCI: 0.4-0,8 mg/h** Rescue (bolus): 2.5-5 mg** Daily maximum: 160-200 mg	Induction (bolus): 1.5-3 mg/ 5 minutes Initial SCCI induction x 6 Rescue (bolus) = induction
Levomepromazine* (ampoules 25 mg/1 ml)	Induction (bolus): 12.5-25 mg Initial SCCI: 100 mg/day Rescue (bolus): 12.5 mg Daily maximum: 300 mg	Normally half the dosage by SC route
Propofol (Rhials 10 mg/ml)	Not used by SC route	Induction (bolus):1-1.5 mg/kg Initial IVCI: 2 mg/kg/h Rescue (bolus): half the induction dosage

* Administration route not contemplated on technical data sheet.
** Double dosage in patients that were already taking BZD.
SCCI: Subcutaneous continuous infusion.
IVCI: intravenous continuous infusion.

After starting the pharmacological treatment the patient's sedation level should be monitored, using instruments such as the Ramsay scale (see table 37) and leaving a record of this on the medical history (326; 330).

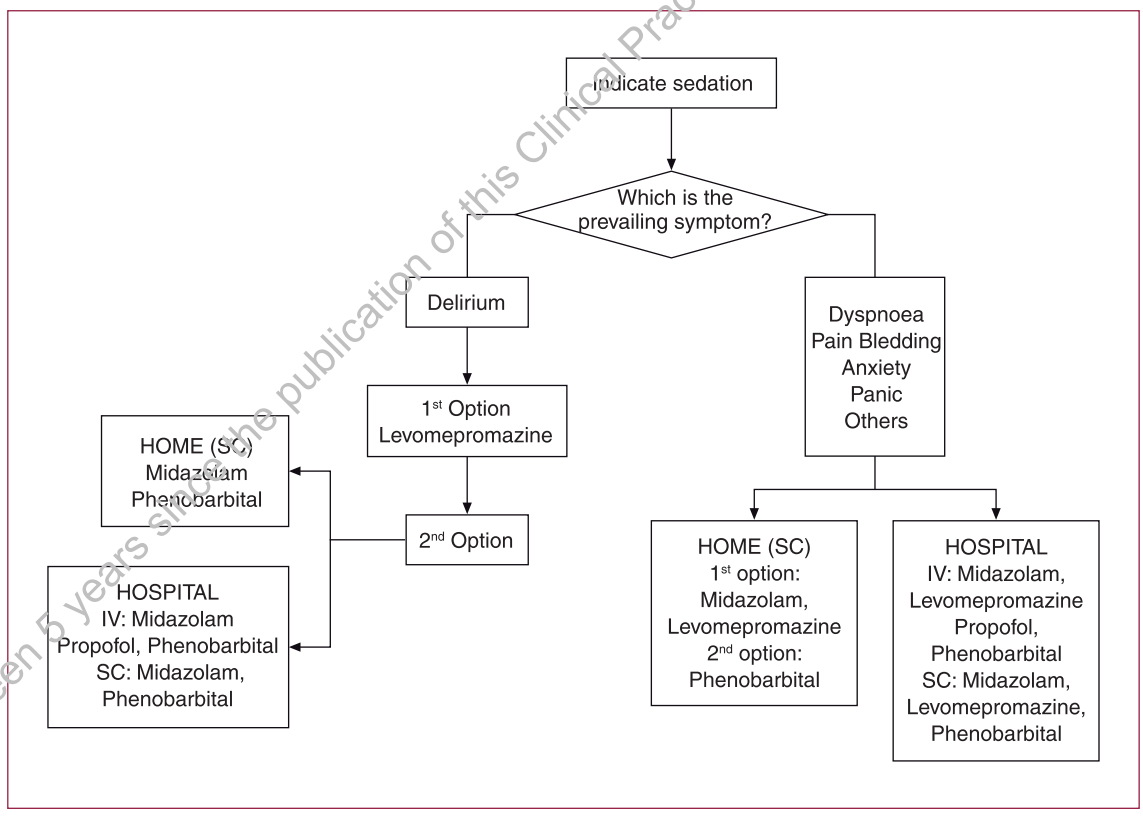
Expert opinion 4

Table 37. Ramsay Scale

Level I	Anxious, agitated patient
Level II	Tranquil, oriented and cooperative patient
Level III	Patient responds to verbal commands
Level IV	Patient with brisk response to glabellar pressure or painful stimulation
Level V	Patient with sluggish response to glabellar pressure or painful stimulation
Level VI	Patient with no response

An algorithm is proposed in figure 13 for the use of drugs in sedation, depending on the prevailing symptoms (326; 330).

Figure 13. Algorithm for the use of drugs in sedation



10.2.5. Ethical and legal considerations

The ethical and legal principles for sedation include (324):

Expert opinion 4

- Appropriate indication and practice
- Intentionality: the objective is to alleviate suffering.
- Principle of proportionality: considering the patient's situation, the intensity of the suffering, the absence of other palliative methods and the estimated survival, sedation is the most proportionate option among other possible ones. It means reaching a balance between the benefits (alleviation of suffering) and the risks and disadvantages (reduction of level of consciousness, effect on survival).
- Principle of autonomy: in agreement with the applicable legislation (331), the patient owns the right to information and is entitled, after receiving the adequate information, to freely decide between the available clinical options. The exceptions are *therapeutic privilege* (express desire of the patient to not be informed or total or almost total convincement that the information represents greater harm for the patient) and the situation of emergency (when there is an immediate serious risk for the physical or psychic integrity of the patient and it is not possible to obtain his or her authorisation). Sedation requires delegated consent when the patient is not competent. It is always recommended to agree to the decisions with the family both if the patient is competent or not.

Legislation LG

Furthermore, the team must decide on the amount of information to be given and how to give it. Information should be given about the voluntary nature of the sedation decision. The team must confirm that the patient's decision is not affected by psychological or social pressure.

Summary of evidence

4	*Palliative sedation* is understood as the deliberate administration of drugs, in the dosage and combinations required to reduce the consciousness of a patient with advanced or terminal illness, as much as necessary to adequately alleviate one or more refractory symptoms, and with his or her explicit consent (326).
4	*Sedation in agony* is a singular case of palliative sedation and is defined as the deliberate administration of drugs to achieve alleviation of a physical or psychological suffering, which is impossible with other measures, via the sufficiently deep and likely irreversible reduction of consciousness in a patient whose death is foreseen to be very near (326).
3	75% to 100% of patients respond to sedation. Midazolam is the most commonly used drug (328).

Recommendations

D	The palliative sedation process or in agony requires: a) A correct therapeutic indication carried out by the doctor (existence of a refractory psychic or physical suffering or symptom at the end of the patient's life), and if possible, validated by another doctor. b) The explicit consent of the patient or family if the patient is incompetent. c) Professionals with clear and complete information about the process, recorded in the medical history. d) Administration of drugs in the necessary dosage and combinations to reach an adequate sedation level.
D	The correct prescription of palliative sedation in agony requires: a) Careful assessment of the end of life diagnosis. b) Presence of refractory psychic or physical suffering or symptoms. c) Assessment of the patient's competence when making decisions.
D LG	Verbal consent is considered sufficient, although it may at times be given in writing. Record must always be kept in the medical history. In non-competent patients, the consent must be given in the following order: a) First, by consulting the Registry of Living Wills or Preliminary Instructions. b) In the absence of preliminary instructions, the medical team must appraise the patient's desires with the family or close friends, considering the previously expressed desires and values. c) In the absence of b), sedation should be agreed with the family.
D	The use of midazolam is recommended as first option for sedation for the majority of the symptoms, and levopromazine when delirium is the prevailing symptom.
D	The use of midazolam is recommended as first option for sedation for the majority of the symptoms, and levopromazine when delirium is the prevailing symptom.

11. Bereavement

The questions that are going to be answered are:

- What is the definition of normal bereavement and what are the phases and signs?
- What is the definition of complicated bereavement and what are the signs?
- What are the risk factors for complicated bereavement and how are they assessed?
- How effective are interventions in normal bereavement, risk bereavement and complicated bereavement?

11.1. Normal bereavement: definition, phases and manifestations

Human *bereavement* is defined as the natural –in agreement with the socio-cultural environment-, normal and expected reaction to adapt to the loss of a loved one (332), suffered by family and friends before, during and after death. It is an experience of total suffering, understanding by this the physical, psycho-emotional, socio-family and spiritual process that the bereaved person undergoes at all those moments; and it includes the series of behavioural, emotional, socio-family and cultural pressures (333; 334).

The bereavement reaction is also characterised for being unique, it is a personal and non-transferable experience; dynamic, changing from one moment to another; and with a complicated chronology, it is difficult to know when it begins and when it ends (332).

Bereavement begins long before death, *anticipated bereavement,* it increases dramatically around the time of death (hours, days), *acute bereavement;* it continues afterwards as *early bereavement* (weeks, months), *intermediate* (months, years) and *late* (years). And it probably never ends, always remaining as an indelible mark on the person, *latent bereavement,* which can be reactivated at any time (332). The first prevailing feature is incredulity; then, the bereaved person suffers and vehemently desires the return of the departed person; then comes anger and fury, and the enormous and deep sadness; finally, and bit by bit, acceptance filters in (335).

Human bereavement is not an illness, but it is an enormous stressing life event; in fact, the death of a son or daughter, or of the spouse, are considered to be the most stressing situations that a person can experience (336; 337).

A very wide range of normal signs can take place during bereavement:

- Physical: loss of appetite, sleep disturbances, loss of energy and exhaustion and different somatic complaints (some related to the illness that the deceased had).

- Behavioural: unease, weeping, tiredness and isolation.
- Cognitive: Obsessive thoughts about the deceased, low self-esteem, self-reproach, feeling of defencelessness, despair, feeling of unreality and problems with memory and concentration.
- Affective: sadness, despair, anxiety, blame, anger and hostility, anhedonia and solitude (338).

It is sometimes associated with health problems, such as depression, generalised anxiety, abuse of alcohol or psychotropic medications; and prolonged bereavement, with an increase in mortality due to suicide and cardiovascular events, and with a greater demand for health support (332).

Most people get over the loss and cope effectively with bereavement *–normal bereavement-,* and some even grow in adversity *–resilience-;* but sometimes the process is especially difficult due to the circumstances *–risk bereavement-* and at times it gets complicated *–complicated bereavement-* (332; 333).

Personality, personal history, experiences related to previous losses or the moment in the person's life are factors that determine the way they express their bereavement and in the subsequent evolution.

Complicated bereavement is considered a reaction of bad adjustment to loss, and can be expressed as a disorder due to prolonged bereavement, depression, anxiety or deterioration of physical health (339).

11.2. Bereavement care: organisation

Expert opinion 4

When bereavement care is planned and organised, the challenge consists in distinguishing between normal and complicated bereavement, and in identifying people with the greatest risk (332; 333; 339). This is justified by the fact that current evidence does not support formal and structured professional intervention in normal bereavement, but those people with risk bereavement could benefit from monitoring or early intervention, and people with complicated bereavement will require specialised support (12; 334; 340-344).

The NICE guideline establishes a bereavement care model with three components, to be implemented in all the British cancer services:

- Support from family and friends is sufficient for most grievers; here the role of professionals is to provide information about bereavement and about the available resources.
- Some grievers require a more formal opportunity to review and reflect on their loss experience; this work can be carried out by volunteers, self-help groups, spiritual advisors, or professionals, who will pay attention to the risk and early detection of problems associated with bereavement in case more specialised care is required.
- A minority of bereaved people will require specialist intervention, which will be provided mainly by mental health, psychotherapeutic or bereavement expert teams.

11.3. Risk factors of complicated bereavement and their appraisal

The risk of suffering complicated bereavement refers to how sensitive the bereaved person is to suffering health problems associated with bereavement (prolonged bereavement, depression, anxiety, etc.).

Expert opinion 4

Identifying the risk forms part of PC. It is a process where risk factors are appraised as well as the probabilities of developing complicated bereavement via the following sources:

- The best available evidence.
- Clinical judgement.
- Information obtained about the family environment or from it. At this point, the genogram can be helpful to know the family structure, its resources and capacities and its possible dysfunctions, and identify the members with the highest risk (340).

The risk assessment not only covers the main carer, but also the closest family members and people who have a significant relationship with the patient. This enables the most intensive bereavement care to be given to the people that most need them (340).

There is a specific guideline about complicated bereavement risk assessment in PC that makes a search and a comprehensive appraisal of this aspect (340).

In agreement with the results of this review and lacking appropriate evidence to perceive the different coping styles, the risk assessment involves four information categories:

1. Characteristics of the illness, terminal care and nature of the death:

SR of different types of studies 2+/3

   - Death is sudden or unexpected, particularly if, a) this has occurred under traumatic circumstances; b) it is stigmatised (suicide, murder, HIV/AIDS); or c) the bereaved person did not have the opportunity to get ready for it or anticipate it.
   - Excessively short illness (bereaved person with feeling of not being prepared).
   - Long illness and middle-aged bereaved person (a long illness may overburden the adjustment mechanisms of family members).

2. Characteristics of the bereaved:

SR of different types of studies 2+/3

   - Stage of life cycle: particularly when the bereaved is an adolescent, a person who widows young or old, or a widowed or separated mother.
   - History of previous losses, particularly if unresolved: infidelity, divorce or loss of a pregnancy.
   - Concurrent stressors: family tensions, economic or work problems, dissatisfaction with care-giving or reliance on alcohol or psychotropic medications.

- Physical or mental illness: particularly mental health problems that have required psychiatric or psychological treatment, or family history of psychiatric disorders.
- High distress during illness or pre-death.
- Poor initial adjustment to the loss, exemplified by intense emotional distress or depression.
- Inability or restriction in use of coping strategies: physical care, identification of prominent themes of the bereavement process, attributing meaning to the loss, modulation of the distressing components of grief, differentiation between *letting go* and *forgetting,* or accessing available support.
- Solitude. Isolated, alienated people.
- Low levels of internal control beliefs; such as feeling as if he/she has no control over life.

3. Interpersonal relationships:

SR of different types of studies 2+/3

- The availability of social support, particularly if the people in the immediate environment are, or are perceived to be unsupportive, or people in the immediate environment are perceived as being antagonistic or unsympathetic.
- The bereaved lacks a confidant with whom to share feelings, concerns, doubts or other existential issues.
- The bereaved experience a disturbance in their social support systems, such as not seeing old friends as often as prior to the death.
- The bereaved is dissatisfied with the help available during the illness.
- Support from family and friends immediately prior to death was good, and following the death it subsided.
- An ambivalent or dependent relationship with the deceased.
- Unusually good, long-term, and relatively exclusive marriages.
- Families with lower levels of cohesion, communication and conflict resolution.

4. Characteristics of the deceased:

Descriptive studies 3

- Child or adolescent.
- Child's death is a result of an inherited disorder or is sudden or violent.
- Parents, adolescents and young adults; particularly if the surviving parent copes poorly.

The importance of the different factors that facilitate bereavement have been studied. These factors would be the following:

Descriptive studies, Expert opinion 3,4

- Positive changes in self-perception: feeling stronger, wiser, more mature and independent, and better able to face other crises; having a better understanding of others; feeling more patient, tolerant, empathic and courageous; and being better able to express emotions, thoughts and feelings.

- Positive changes related to social support: bonds with family and friends are reinforced, with more positive experiences with the social support system. Furthermore, optimism and hope also help coping easier (340).

Diagnostic test studies

Some attempts have been made to construct instruments to measure the complicated bereavement risk such as the Index Risk of Parkes and Weiss (345) (see appendix 2), adapted to Spanish by García *et al*. (346); but a lot more studies are required in this area. The Aranda & Milne guideline recommends the clinical judgement of the professional, as the main prognostic element, and the review of a list that includes the risk factors mentioned above (340).

11.4. Complicated bereavement or disorder due to prolonged bereavement

Expert opinion 4

Approximately 10 to 20% of the bereaved find considerable difficulties in adjusting to the loss (344).

Complicated bereavement is often difficult to distinguish from depression, anxiety or post-traumatic stress disorder, illnesses often associated with bereavement and whose symptoms overlap, so its definition is very controversial (344; 347).

The criteria given below, proposed by Prigerson *et al*. (347) for inclusion in the fifth version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) of the American Psychiatric Association, in an attempt to achieve recognition of complicated bereavement as a specific mental disorder and not as a subcategory, as currently occurs in the *DSM-IV,* can be used to diagnose complicated bereavement –now called *Disorder due to Prolonged Bereavement*-:

1. Criterion A. Present at least one of the following systems on a daily basis:
   - Intrusive thoughts (that enter the mind without control) about the diseased.
   - Pangs of uncontrollable grief related to the separation.
   - Intense yearning (recall the absence with an enormous and deep sadness) for the person who has died.
2. Criterion B. Have at least five of the following nine symptoms on a daily basis:
   - Confusion about one's role in life or feeling that a part of oneself has died.
   - Difficulty accepting the loss as real.
   - Attempt to avoid reminders of the reality of the loss.
   - Inability to trust others since the loss.
   - Bitterness or anger related to the loss.
   - Difficulty moving on with life (e.g. making new friends or pursuing new interests).

- Numbness (absence of emotion) since the loss.
- Feeling that life is unfilling, empty and meaningless, since the loss.
- Feeling «stunned», dazed or shocked.

3. Criterion C. Duration of these symptoms is at least six months.
4. Criterion D. These symptoms cause clinically significant stress or impairment in social, occupational or other important areas of functioning (e.g. domestic responsibilities) of the bereaved person.

11.5. Efficiency of interventions in bereavement

SR of RCT intervention studies 1+/2+

There are several systematic reviews on the efficiency of interventions in bereavement; most of them include studies with methodological problems (few subjects, no random allocation, confusion factors, etc.) and they have enormous heterogeneity in study populations (they include people in normal risk and complicated bereavement) and in the interventions. However, it must be highlighted that the results obtained in the different systematic reviews are quite consistent.

35 studies were included in the meta-analysis of Allumbaugh & Hoyt (348) (13 without control group and 22 with control group and random allocation), 2284 subjects, 84% women and the average time since death was 27 months. The intervention effect size (individual, group, etc.) was moderate, with a standardised difference of means of 0.43 (IC 95%: 0.33-0.52). The authors concluded the following in their review:

The intervention effect size in bereavement is small if compared with other psychotherapeutic techniques.

The best results are obtained in the intervention studies when it is the actual bereaved person who asks for help and when the intervention begins a few months after the loss.

SR of RCT and intervention studies 1+/2+

The doctoral thesis of Von Fortner (342), based on the limited efficiency found, concludes the following:

Psychological counselling or other forms of psychosocial therapy have no justification in people with normal bereavement; they may even be harmful. They seem to be helpful in people with risk bereavement or complicated bereavement.

SR of RCT and intervention studies 1+/2+

The results of subsequent SR are similar. The review of Genevro *et al*. (333) concludes the following:

Interventions on adults with normal bereavement «cannot be considered beneficial in terms of reducing the symptoms related to the bereavement », and may even be harmful.

Interventions on adults with risk bereavement provide some benefit, at least in the short term.

There is not a lot of evidence in adults with complicated bereavement, but the analysis of the data reflects a positive effect with psycho-dynamic or cognitive-behavioural orientation therapies; and in the case of depression associated with bereavement with tricyclic antidepressants (nortriptyline) and psychotherapy.

In children and adolescents, strategies such as providing information and education in bereavement, opportunities to express their feelings and understand them, remembering and commemorating the anniversary of the death, and facilitating and improving communication in the family seem to be efficient, especially in girls.

The review by Forte *et al*. (341) concludes the following:

There is good evidence in favour of pharmacological treatment of depression in bereavement.

There are no consistent treatments patterns for other intervention methods that reduce the bereavement per se.

The review by Wimpenny *et al*. (334) concludes the following:

Most bereaved do not require professional psychological counselling.

This may be beneficial in unexpected, traumatic deaths or with little socio-family support.

The interventions assessed in the different studies vary a good deal:

SR of RCT and intervention studies 1+/2+

Group interventions: self-help groups, individual programmes,

(*widow to widow*), volunteers, individual, family, couple and group psychological counselling, etc.

Psychotherapeutic interventions: cognitive-behavioural (cognitive restructuring, problem-solving desensitisation, etc.), psycho-dynamic, psycho-analytical, interpersonal, group therapies, etc.

Psychopharmacological interventions: tricyclic antidepressants and benzodiazepines.

However, it is impossible to obtain clear conclusions from the available evidence about which is the most efficient intervention in bereavement, with the exceptions of psycho-emotional counselling in bereavement in children or adolescents and risk bereavement in adults, psychodynamic or cognitive-behavioural psychotherapy in complicated bereavement in adults, or antidepressants combined with psychotherapy in depression associated with bereavement (333; 334; 341; 344).

A recent clinical trial (349) has been conducted at several intensive care units in France, in which the efficiency of a structured meeting (approximately 30 minutes long) of trained ICU staff, with the support of psychologists, with family members of a patient in EOL is verified, as well as the presentation of an information leaflet about bereavement, obtaining positive results 60 days after the death.

RCT 1+

Summary of evidence

2+	Most people cope effectively with bereavement, but 10% - 20% of the people have considerable difficulties in their adjustment process (333; 334; 344).
2+	The assessment of the risk factors implies four information categories (340): a) Characteristics of the illness, of the PC and nature of death b) Characteristics of the bereaved c) Interpersonal relationships d) Characteristics of the deceased
1+/2+	Interventions in normal bereavement are not efficient, they may even be harmful; in risk bereavement there can be a certain benefit; and in complicated bereavement they are efficient (333; 334; 342; 344; 348).
1+/2+	The interventions assessed in the different studies are very variable, but the available evidence is not sufficient to conclude which is the most efficient therapy, except for psychological advice in bereavement in children and adolescents and in risk bereavement, psychodynamic and cognitive-behavioural orientation therapies in complicated bereavement, and psychotherapy together with antidepressants in depression associated with bereavement (333; 334; 342; 344; 348).

Recommendations

D	The risk of complicated bereavement should be identified based on the following: a) Risk factors. b) Clinical judgement. c) Information about the family environment (genogram) or originating from this. Studies are required to appropriately evaluate the validity of the available scales (such as the Parkes & Weiss Risk Index).
B	Formal or organised interventions are not recommended in normal bereavement.
D	In normal bereavement it is recommended to provide information about bereavement and about the available resources, and basic emotional support.
B	In risk bereavement it is recommended to carry out regular monitoring, with emotional support, individually evaluating the need for specific and structured psychotherapies.
B	It is recommended to refer the person with complicated bereavement to specialised services (psychology, psychiatry, etc.) to receive specific and structured care.
D	Professionals caring for patients in EOL and their relations should have access to elementary training in bereavement to qualify them to provide basic care to the bereaved, understand and explore their needs, evaluate risk factors, and detect people with complicated bereavement and refer them to a specialised service.

Appendices

Appendix 1. Levels of scientific evidence and grades of recommendation SIGN

Levels of scientific evidence	
1++	High quality meta-analysis, systematic reviews of clinical trials, or clinical trials with a very low risk of bias.
1+	Well-conducted meta-analysis, systematic reviews of clinical trials or well-conducted clinical trials with a low risk of bias.
1-	Meta-analysis, systematic reviews or clinical trials with a high risk of bias.
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of bias and a high probability that the relationship is causal.
2+	Well-conducted case control of cohort studies with a low risk of bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytic studies, such as case reports and case series.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, systematic review or clinical trial rated as 1++ and directly applicable to the target population or the guideline; or a body of evidence consisting of studies rated as 1+ and demonstrating overall consistency of results.
B	A body of scientific evidence including studies rated as 2++, directly applicable to the target population of the guideline, and demonstrating overall consistency of results; or extrapolated scientific evidence from studies rated as 1 ++ or 1+.
C	A body of scientific evidence including studies related as 2+, directly applicable to the target population of the guideline and demonstrating overall consistency of results; or extrapolated scientific evidence from studies rated as 2 ++.
D	Scientific evidence level 3 or 4; or extrapolated scientific evidence from studies rated as 2+.

The studies rated as 1- and 2- must not be used in the recommendations preparation process due to their high possibility of bias.

Best clinical practice

√[1]	Recommended practice based on the clinical experience of the guideline development group.

[1] *At times, the development group finds important practical aspects that must be highlighted and for which no scientific evidence has been found. In general, these cases are related to some aspect of the treatment that nobody would normally question and they are evaluated as points of best clinical practice. They are not an alternative to the recommendations based on scientific evidence, but rather they must only be considered when there is no other way of highlighting this aspect.*

Appendix 2. Scales

Edmonton Symptom Assessment System (ESAS)

Edmonton Symptom Assessment Scale

List of 10 numerical scales that assess the average intensity of different symptoms in a specific time interval (24 hours, 48 hours, 1 week), according to the patient's condition. The patient is asked to select the number that best indicates the intensity of each symptom.

Minimum symptom	Intensity	Maximum symptom
No pain	0 1 2 3 4 5 6 7 8 9 10	Worst possible pain
Not tired	0 1 2 3 4 5 6 7 8 9 10	Worst possible tiredness
No nausea	0 1 2 3 4 5 6 7 8 9 10	Worst possible nausea
Not depressed	0 1 2 3 4 5 6 7 8 9 10	Worst possible depression
Not anxious	0 1 2 3 4 5 6 7 8 9 10	Worst possible anxiety
Not drowsy	0 1 2 3 4 5 6 7 8 9 10	Worst possible drowsiness
Best appetite	0 1 2 3 4 5 6 7 8 9 10	Worst possible appetite
Best feeling of well-being	0 1 2 3 4 5 6 7 8 9 10	Worst poss. feeling of well-being
No shortness of breath	0 1 2 3 4 5 6 7 8 9 10	Worst poss. shortness of breath
No difficulty to sleep	0 1 2 3 4 5 6 7 8 9 10	Worst poss. difficulty to sleep

Palliative Prognostic Score (PaP Score)

Variable	Score
Dyspnoea	
Present	1
Absent	0
Anorexia	
Present	1.5
Absent	0
Clinical prediction (weeks)	
>12	0
11-12	2
9-10	2.5
7-8	2.5
5-6	4.5
3-4	6
1-2	8.5
Karnofsky performance status	
≥30	0
10-20	2.5
Total leucocytes per mm^3	
≤8,500	0
8,501-11,000	0.5
>11,000	1.5
Lymphocyte percentage	
<12	2.5
12-19.9	1
≥20	0
Risk Groups	**Total score**
A (30-day survival probability >70%)	0 - 5.5
B (30-day survival probability 30-70%)	5.6 - 11
C (30-day survival probability <30%)	11.1 - 17.5

Karnofsky functional performance scale

Objectives of the Karnofsky functional performance scale

- It helps discover the patient's ability to carry out activities of daily living.
- It is an independent mortality prediction element in oncological and non-oncological pathologies.
- It is helpful to make clinical decisions and evaluate the impact of a treatment and the progression of the patient's disease.
- A Karnofsky of 50 or less indicates a high risk of death in the following six months.

Scale	Functional evaluation
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs and symptoms of disease
80	Normal activity with effort, some signs and symptoms of disease
70	Cares for self, but unable to carry on normal activity or do work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care. Confined to bed for less than 50% of the day
40	Disabled, requires special care and assistance. Confined to bed more than 50% of the day
30	Severely disabled, requires active support treatment
20	Totally confined to bed, very sick, hospitalisation and active treatment necessary
10	Moribund
0	Dead

Barthel Scale – Basic activities of daily living

It assesses the functional situation of the person via a scale that measures the ADL (Activities of daily living)

It is the most commonly used internationally and it is one of the best instruments to monitor the functional dependence of people

It assesses 10 kinds of activities and classifies five groups of dependence.

It is easy and quick to use and it is the most dynamic to be used statistically.

Objectives of the Barthel scale

- Assess the functional ability.
- Detect the degree of deterioration.
- Objectively monitor the clinical evolution.
- Design care and rehabilitation plans in an interdisciplinary manner.

Barthel Scale

Activity	Appraisal
Feeding	10 independent 5 needs help 0 dependent
Washing	5 independent 0 dependent
Grooming	5 independent 0 dependent
Dressing	10 independent 5 needs help 0 dependent
Bladder	10 continent 5 occasional accident 0 incontinent
Bowels	10 continent 5 occasional accident 0 incontinent
Toilet use	10 independent 5 need help 0 dependent
Transfers (bed to chair and back)	15 independent 10 minor help 5 major help 0 dependent
Mobility	15 independent 10 needs help 5 wheelchair independent 0 dependent
Going up and down stairs	10 independent 5 needs help 0 dependent

Total Score

100	≥60	55/40	35/20	<20
Independent	Slightly dependent	Moderately dependent	Severely dependent	Totally dependent

Score: Each activity is scored with an interval of 5 points (0, 5, 10, 15). The maximum score will be 100, and this indicates independence for personal care, but it does not mean that the patient can live alone.

Activities of daily life

Feeding:

- Independent: able to use any necessary device, able to cut up food, spread butter, use condiments, etc. On his own. Eat in a reasonable time. Food may be cooked and served by another person. (10)
- Need help: to cut meta or bread, spread butter, etc, but is able to feed self. (5)
- Dependent: needs to be fed by another person. (0)

Washing (bathing):

- Independent: able to wash self all over, may be in shower, full bath or standing and sponging all over the body. Includes getting into and out of bath. Able to do all of this without the presence of another person. (5)
- Dependent: Needs help or supervision. (0)

Grooming:

- Independent: carries out all personal activities without any help. Includes washing hands and face, combing hair, putting makeup on, shaving and clearing teeth. The implements required to do so may be provided by another person. (5)
- Dependent: Needs some help. (0)

Dressing:

- Independent: able to dress and undress, tie shoe laces, fasten buttons and put on other accessories without help. (10)
- Needs help: but do at least half the tasks unaided in a reasonable time. (5)
- Dependent. (0)

Bladder:

- Continent: no incontinency episodes (dry day and night). Able to use any device. In patients with catheter includes being able to change bag alone. (10)
- Occasional accident: Maximum once in 24 hours, includes needing help with handling catheters or devices. (5)
- Incontinent: includes patients with catheter unable to manage alone (0)

Bowels:

- Continent: no incontinency episode. If needs to be given enema or suppository is able to administer them alone. (10)
- Occasional accident: less than once a week or needs help to manage enemas or suppositories. (5)
- Incontinent: Needs another person to be given enemas or suppositories. (0)

Toilet use:

- Independent: goes in and out alone. Able to dress and undress, wipe self, avoid stains on clothing and pull the chain. Able to get on and off the toilet alone (can use bars for balancing). If use commode (urinary, bottle, etc.) able to use it and empty it completely unaided and without getting soiled. (10)
- Needs help: able to manage with minor help balancing, dressing and undressing, but can wipe self. Still able to use toilet. (5)
- Dependent: unable to manage without major assistance. (0)

Transfers bed to chair and back:

- Independent: no help in any of the phases. If using wheelchair includes bring it close to the bed, locking, moving footrest, closing chair, get into sitting position on one side of the bed, get in and lie down, and can return to the chair without help. (15)
- Minor help: includes verbal supervision or minor physical aid, such as that offered by a person who is not particularly strong or has no training. (10)
- Major help: able to sit without help, but needs major assistance (strong and trained person) to get out / get onto be or move (5)
- Dependent: needs hoist or complete life by two people. Unable to remain seated. (0)

Mobility:

- Independent: can walk for at least 50 metres or equivalent at home without help or supervision. The speed is not important. May use any aid (stick, crutch, etc.) except walking frame. If uses prosthesis is able to put it on and take it off alone. (15)
- Needs help: supervision or minor physical aid (person not necessary strong) to walk 50 metres. Includes instruments or aids to stand (walking frame) (10)
- Independent in wheelchair in 50 metres: has to be able to move, go through doors and go round corners alone (5)
- Dependent: if uses wheelchair needs another person to manage it. (0)

Going up and down stairs:

- Independent: able to go and down one flight of stairs without aid or supervision. May use walking aid if necessary (stick, crutch), and banister. (10)
- Needs help: verbal or physical supervision. (5)
- Dependent: cannot negotiate stairs. Needs lifting (lift). (0)

Palliative Care Scale (ECP) – *Spanish Version of the Palliative Care Outcome Scale (POS)*

HEALTH STAFF QUESTIONNAIRE

Patient name .....
Unit or Service ..... Date of birth .....
Date ..... Assessment no. .....

Please answer the following questions by ticking the box next to the answer which you think most accurately describes how the patient has been feeling. Thank you.

1. Over the past 3 days, has the patient been affected by pain?
- ☐ 0 Not at all.
- ☐ 1 Slightly, but not bothered to alleviate it.
- ☐ 2 Moderately, pain limits some activities.
- ☐ 3 Severely, activities or concentration markedly affected by pain
- ☐ 4 Overwhelmingly, the patient is unable to think of anything else.

2. Over the past 3 days, have any other symptoms e.g. nausea, coughing or constipation seemed to be affecting how the patient feels?
- ☐ 0 No, not at all.
- ☐ 1 Slightly.
- ☐ 2 Moderately.
- ☐ 3 Severely.
- ☐ 4 Unsupportable.

3. Over the past 3 days, has the patient been feeling anxious or worried about his or her illness or treatment?
- ☐ 0 No, not at all.
- ☐ 1 Occasionally.
- ☐ 2 Sometimes, it affects their concentration now and again
- ☐ 3 Most of the time, it often affects their concentration.
- ☐ 4 Yes, they feel anxious all the time.

4. Over the past 3 days, have any of their family or friends been anxious or worried about the patient?
- ☐ 0 No, not at all.
- ☐ 1 Occasionally.
- ☐ 2 Sometimes, it affects their concentration now and again.
- ☐ 3 Most of the time, it often affects their concentration.
- ☐ 4 Yes, they feel anxious all the time.

5. Over the past 3 days, how much information has been given to the patient and their family or friends?
- ☐ 0 Full information, the patient feels free to ask
- ☐ 1 Information given, but not always understood by patient.
- ☐ 2 Information given to patient on request, but patient would have liked more.
- ☐ 3 Very little given and some questions have been avoided.
- ☐ 4 None at all.

6. Over the past 3 days, has the patient been able to share how they are feeling with family or friends?
- ☐ 0 Yes, as much as they wanted to.
- ☐ 1 Most of the time.
- ☐ 2 Sometimes.
- ☐ 3 Occasionally.
- ☐ 4 No, not at all with anyone.

7. Over the past 3 days, do you think the patient has felt that life was worth living?
- ☐ 0 Yes, all the time.
- ☐ 1 Most of the time.
- ☐ 2 Sometimes.
- ☐ 3 Occasionally.
- ☐ 4 No, not at all.

8. Over the past 3 days, do you think the patient has felt good about himself or herself?
- ☐ 0 Yes, all the time.
- ☐ 1 Most of the time.
- ☐ 2 Sometimes.
- ☐ 3 Occasionally.
- ☐ 4 No, not at all.

9. Over the past 3 days, how much time do you feel has been wasted on appointments relating to the healthcare of this patient, waiting around or repeating tests?
☐ 1 None at all.
☐ 2 Up to half a day wasted.
☐ 3 More than half a day wasted.

10. Over the past 3 days, have any practical matters resulting from their illness, either financial or personal been addressed?
☐ 0 Practical problems have been addressed and they have been carried out as the patient wished.
☐ 1 Practical problems are in the process of being addressed.
☐ 2 Practical problems exist which were not addressed.
☐ 3 The patient had had no practical problems.

11. If any, what have been the patient's main problems in the last 3 days?
1 .....
2 .....

12. What is the patient's ECOG scale performance status?
(0: fully active; 1: restricted; 2: ambulatory; 3: limited self-care; 4: completely disabled)

Visual Analogue Scale (VAS)

The **Visual Analogue Scale (VAS)** permits measuring the intensity of the pain described by the patient with maximum reproducibility among the observers. It consists of a 10 centimetre horizontal line with extreme expressions of a symptom at both ends. The absence of less intensity is on the left and the greatest intensity on the right. The patient is asked to mark on the line the point that indicates the intensity and this is measured with a ruler. The intensity is expressed in centimetres or millimetres.

No pain _____ Very severe pain

The **Numerical Scale (NS)** is a set of numbers from zero to ten, where zero marks the absence of the symptom to be assessed and ten is the greatest intensity. The patient is asked to select the number that best indicates the intensity of the symptom that is being assessed. This is the simplest method to interpret and the most commonly used.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Very severe pain

The **Categorical Scale (CS)** is used when the patient is not able to quantify his or her symptoms with the previous scales, expressing the intensity of the symptoms in categories, which is much simpler. A relationship is usually established between categories and a numerical equivalent.

0	4	6	10
None	Mild	Moderate	Severe

The **Visual analogue pain intensity scale** consists in a horizontal straight line, 10 cm long, where the ends mark the severity of the pain. The absence of pain appears on the left and the worst pain imaginable appears on the right.

0	1	2	3	4	5	6	7	8	9	10
None										Intolerable

The **Visual analogue pain improvement scale** consists in the same straight line, where no improvement appears on the left and full improvement on the right.

0	1	2	3	4	5	6	7	8	9	10
No improvement										Full improvement

Brief Pain Questionnaire (BPQ)

1. On the diagram shade in the areas where you have pain. Put an X on the area that hurts the most.

Front: Right / Left — Back: Left / Right

2. Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

3. Please rate your pain by circling the one number that best describes your pain at its least in the last week.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

4. Please rate your pain by circling the one number that best describes your pain on the average in the last week.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

5. Please rate your pain by circling the one number that best describes how much pain you have right now.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

6. What kinds of things make your pain feel better (e.g. walking, standing, lifting something)?

_____

_____

7. What kinds of things make your pain worse (e.g. walking, standing, lifting something)?

_____

_____

8. What treatments or medications are you receiving for the pain?

_____

_____

9. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

No relief 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Total relief

10. If you take pain medication, how many hours does it take before the pain returns?

1. ☐ Pain medication does not help at all
2. ☐ 1h
3. ☐ 2h
4. ☐ 3h
5. ☐ 4h
6. ☐ 5 to 12h
7. ☐ More than de 12h
8. ☐ I do not take pain medication

11. Check the appropriate answer for each item.

I believe my pain is due to:

☐ Yes ☐ No A. The effects of the treatment (e.g. medication, surgery, radiation, prosthesis)

☐ Yes ☐ No B. My primary disease (meaning the disease currently being treated and evaluated)

☐ Yes ☐ No C. A condition unrelated to my primary disease (e.g. arthritis)

Please describe this condition: _____

12. For each of the following words, check Yes or No if that adjective applies to your pain.

Aching	☐ Yes ☐ No	Cramping	☐ Yes ☐ No
Throbbing	☐ Yes ☐ No	Acute	☐ Yes ☐ No
Shooting	☐ Yes ☐ No	Tender	☐ Yes ☐ No
Sharp	☐ Yes ☐ No	Burning	☐ Yes ☐ No
		Exhausting	☐ Yes ☐ No
Tiring	☐ Yes ☐ No	Numb	☐ Yes ☐ No
Penetrating	☐ Yes ☐ No	Miserable	☐ Yes ☐ No
Nagging	☐ Yes ☐ No	Unbearable	☐ Yes ☐ No

13. Circle the one number that best describes how, during the past week, pain has interfered with the following aspects of your life.

A. General Activity

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

B. Mood

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

C. Walking ability

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

D. Normal work (includes both work outside the home and housework)

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

E. Relations with other people

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

F. Sleep

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

G. Enjoyment of life

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

14. I prefer to take my pain medicine:

1. ☐ On a regular basis
2. ☐ Only when necessary
3. ☐ I do not take pain medicine

15. I take my pain medicine (in a 24 hour period):

1. ☐ Not every day
2. ☐ 1 to 2 times a day
3. ☐ 3 to 4 times a day
4. ☐ 5 to 6 times a day
5. ☐ More than 6 times a day

16. Do you feel you need a stronger type of pain medication?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

17. Do you feel you need to take more of the pain medication than your doctor has prescribed?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

18. Are you concerned that you use too much pain medication?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

If Yes, why?

_____

_____

19. Are you having problems with side effects of your pain medication?

1. ☐ Yes 2. ☐ No

¿Which side effects?

_____

20. Do you feel you need to receive further information about your pain medication?
1. ☐ Yes 2. ☐ No

21. Other methods I use to relieve my pain include (please check all that apply):
Warm compresses ☐ Cold compresses ☐ Relaxation techniques ☐
Distraction ☐ Biofeedback ☐ Hypnosis ☐
Others ☐ Please specify _____

22. Medications not prescribed by my doctor that I take for pain are:
_____

Ramsay Scale

Level I	Anxious, agitated patient
Level II	Tranquil, oriented and cooperative patient
Level III	Patient responds to verbal commands
Level IV	Patient with brisk response to glabellar pressure or painful stimulation
Level V	Patient with sluggish response to glabellar pressure or painful stimulation
Level VI	Patient with no response

Appendix 3. Breaking bad news: Buckman's six-step protocol

Step 1. Preparing the most adequate physical context

This stage will include all the aspects related to the most adequate time, place, practitioner, patients, as well as a short evaluation of the patient's emotional status to find out if it is the right moment to break the bad news; for example, *How are you today?* Or *How are you, how are you feeling?* Or *Do you feel well enough to have a short talk?* (depending on the situation, one of these questions or similar ones will be chosen).

Step 2. Finding out how much the patient knows

This phase is very important, as the patient often has ideas or at least suspicions that may save the practitioner a lot (imagine a patient who smokes who has been admitted because they saw «something» in his or her lung and thousands of tests have been carried out in the hospital including a bronchoscopy). The information provided and the impact that this may produce will depend to a great extent on how well this phase is executed.

This is done via open ended indirect questions and active listening with narrative support techniques, concentrating the attention not only on the patient's narration but also on his o her non-verbal communication. It is particularly interesting to know how serious the patient believes his or her process is and how it can affect their future. These aspects are of much greater interest than knowing the name of their illness or their pathophysiology. Of course it is not advisable «to spend time» on aspects that have no importance in the patient's or family's evolution or are not necessary to understand the process.

Here are some of the questions that can be used:

— *What do you think about this problem, the pain in your chest, your cough, etc, etc.?*

— *What have you been told about your illness?*

(This question is very positive in order to avoid misunderstandings or contradictory messages or with different nuances, which is a relatively frequent problem in patients who are cared for by different practitioners in different settings: cancer patients, etc):

— *What do you believe your problem may be due to?*

— *Have you considered that this may be serious?*

It may even be advisable to ask these questions in a staggered fashion, leaving the last one mentioned, for example, until the end of this phase, when we have already captured some of the patient's beliefs.

We can obtain information from the patient on different aspects with this kind of question:

- How close his or her impression is to the real nature of the problem.
- Patient's characteristics: education level, expression capacity, preparation, etc.
- Emotional state in connection with the process. It is advisable to pay attention to what thepatient says and what he or she does not say and avoids saying, as well as all the non-verbal keys that we are able to capture. It is interesting to notice the lack of consistency between non-verbal and verbal communication.

On the other hand, asking people, who do not suspect anything, this type of question may help them get acclimatised to the new situation.

Once we have explored what they already know, we must find out what they suspect. If this has not come out with any of the previous questions, some of the following can be added:

— *And why do you believe that all these tests have been done?*

— *And what exactly are you concerned about?*

— *Are you concerned about...?*

— *Is there something that concerns you?*

In a second phase we can introduce questions about the future, above all in those patients that we suspect know nothing about the nature of their problem. For example: *What plans have you got for the future?* The aim of this question is to minimise uneasiness as much as possible and transmit to the patient the fact that we are interested in how he or she feels and thinks, and are willing to listen to them.

We must bear in mind that the professional is not the only means of information. The patient receives information through other patients, from diagnostic or therapeutic means, other practitioners or from the media.

Another added advantage of correctly executing this phase is avoiding the more or less contradictory messages that often occur among different professionals, either due to different criterion, fear of telling the truth, lack of security or lack of knowledge.

Step 3. Finding out how much the patient wants to know

This phase is essential when sharing subsequent information with the patients. It is sometimes difficult to know if the patient wants to know and if we are giving too much or too little information. In other words, it is difficult to know how much information the patient is able to assimilate at each interview.

We advise asking directly what level of information they can assimilate. For example: *If this should, by chance, turn into something serious, are you the kind of person who would like to know exactly what it is? Would you like me to explain all the details of the diagnosis to you? Are you the kind of person who would like to know all the details about the diagnosis or would you prefer to just know the treatment to be followed? If the problem is serious, how much would you like to know about it? Or, Would you like me to explain all the details about your problem or is there someone else who you would like me to talk to about it??*

Some of these questions let the patient choose. Namely, questions such as *Are you the kind of person...?* *acknowledges* that there are people like that and it makes it easier for you to recognise their posture if they do not want information. Or, on the other hand, the possibility is left open in the last question to move the weight of the information to another person of the environment.

This type of question may seem to «reveal» information or may even cause more stress in the actual patients, but the truth is that if it is done well, it may clear up a lot of things for the professional, but without causing harm to the patient.

In any case, as mentioned above, it is not necessary to ask so openly to find out if a patient wants to know and how much they want to know. If the professional is sensitive enough the same information can be obtained. In our culture, one option can be to wait for the patient to ask us for more information, paying a lot of attention to non-verbal communication, waiting for the patient to assimilate each «part» of the information that has been given with silences and active listening,

and to ask us for more by looking at the professional in an expectant manner or directly asking for more information with questions. A useful simile could be giving them a piece of cake (small so it is not too difficult to digest) and wait for them to assimilate it and ask us for more pieces, in agreement with their own assimilation rate.

If the patient expresses his or her preference to not discuss the matter or leads us to believe that, we must always leave the door open, as some of them may change their minds later on. But respect for the patient's decision must be obvious.

Step 4. Sharing the information

If, in the previous phase, the patient has expressed his or her desire to share all the information we will proceed to do this. If the patient has said he or she does not, we can go on to discuss the treatment plan.

Providing information here played a dual role: for the patient to know about the process and hold a therapeutic dialogue.

First of all we must «align up» with the patient, based on the level of information they already have. Then decide on the objectives of the interview: what information and educational aspects are going to be dealt with. It is essential to have a clear agenda, always very open to the agenda of the actual patient. Based on this we will start to address elements of the diagnosis, treatment, prognosis or support of the patient depending on the needs.

It is important in this phase to be aware of the patient's right to make his or her own decisions, mainly in connection with the treatment, and for this not to generate frustration in the professional if the decision does not coincide with his or her way of seeing the situation.

As it has already been implied, this phase can be simultaneous to the previous stage. The patient's request for more information will tell us his or her capacity to assimilate and will enable us to decide how much information we must give them.

Step 5. Responding to the patient's feelings

This consists basically in identifying and recognising the patients' reactions. Well-delivered bad news can fail if the professional does not develop this phase appropriately.

The role of silences, non-verbal empathy and listening and respect for the patient are also important elements to be highlighted here.

Step 6. Planning and follow-through

The follow-through must be agreed by both. Professionals must make it clear to the patient that they will always be at his or her disposal when required. They must continuously pay attention to the patient's problems or concerns and also mobilise all the family or social support sources required at each moment. In this regard, it must be taken into account that this kind of patient generates real feelings of solitude as they do not share their concerns and fears with other family members or friends so as not to make them suffer. The continuity of our care must be made clear in these communication aspects as well as in the physical process.

Attitude must obviously be positive, preparing them for the worst when this possibility exists and expecting the best, without false expectations and without providing unreal information.

A certain strategy must be planned related to the number of visits, treatment phases, etc. The patient must see that we control the situation.

Evaluation of the strategies used

This section is extremely important, as an analysis of the interviews held with advantages and defects helps the professional get to know himself better and reaffirm his confidence. It can also provide instruments to improve any necessary aspects.

A good way of evaluating the strategy used is to appraise our emotions, ideas or actions after the interview via personal reflection. We must appraise what we have felt, our security and «comfortability», the impact that we have produced and the reactions, if the information the patient has assimilated was as expected and if the patient's objectives with respect to the future are clear.

In this sense, it can be very useful to verify the assimilation quite frequently during the interview and ask the patient for a final summary and his or her emotional status after the interview; a simple *How do you feel?* The comments to this question can give us quite a real appraisal of the quality of the interview and fulfilment of objectives. The information provided by close friends and relations about the patient's subsequent mood and attitude can also help appraise our intervention as well as give us important information with respect to the follow-through of the patient.

The development of this appendix has been based on the following references:

1. Prados Castillejo JA, Quesada Jiménez F. Guía práctica sobre cómo dar malas noticias. FMC. 1998; 5(4): 238-50
2. Buckman R How to break bad news. A guideline for health care professionals. Baltimore: Ed. John Hopkins, 1992.
3. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist. 2000;5(4):302-11.

Appendix 4. Legal aspects in palliative care

General regulation framework

It is compulsory for the State to protect the dignity of is members and penalise anyone not respecting this. It is also compulsory for it to create the conditions to develop it and promote it, fostering an equitable society where no person is marginalised, discriminated or segregated, and no person is placed in a situation of lack of dignity. In these conditions, a society that seeks to procure death, arguing respect for the patient's will would be as immoral as a society that forbids it without providing any solution to the harm and injustice of its citizens[9].

Different laws that affect the clinical relationship at the end of life have been referred to throughout the different chapters of this guideline. Some of the laws that may affect the people who intervene in the care of patients at the end of life are listed below:

International Standards

1. The Convention of Oviedo.
2. The Universal Declaration of Human Rights proclaimed by the General Assembly of the United Nations, 10 December 1948.
3. Convention for the Protection of Human Rights and of Fundamental Freedoms, 4 November 1950.
4. European Social Charter, 18 October 1961.
5. International Covenant on Civil and Political Rights, and the International Covenant on Economic, Social and Cultural Rights, 16 December 1966.

National Standards

1. Spanish Constitution.
2. Criminal Code (assistance to suicide, omission of the duty to help, coercions, homicide by imprudence).
3. General Health Act (with Spanish acronym, LGS).
4. Law 41/2002, Basic Law regulating the patient's autonomy and the rights and obligations related to information and clinical documentation.
5. Law 16/2003, 28 May: Law of cohesion and quality of the National Health System.
6. Law 44/2003, 21 November: Organisation of health professions.
7. Laws enacted in different Autonomous Communities that contemplate Living Wills (LW) or Preliminary Instructions (PI).
8. Deontological Codes.

[9] Couceiro A. El enfermo terminal y las decisiones en torno al final de la vida. In: Couceiro A, editor. Ética en Cui- dados Paliativos. Madrid: Editorial Triacastela; 2004. p. 426.

Euthanasia and assisted suicide

An important amendment was introduced into our criminal code in 1995 in connection with euthanasia and assisted suicide: section four of article 143, referring only to the *active* cooperation, in other words, to actions and not to omissions. That is why *passive* collaboration, when carried out after the serious and unequivocal request by a patient suffering a serious disease, which is necessarily going to lead to his or her death, or which produces serious permanent suffering that is difficult to support, is free from criminal responsibility. In other words, our code legalises what is known as passive euthanasia and continues to penalise direct active euthanasia.

Spanish Criminal Code. Taken from Azucena Couceiro[9]

Article 143	Consequences
1. Any person *inducing to suicide* will be punished with 4 to 8 years in prison. 2. A 2 to 5 year prison sentence will be imposed on anyone cooperating in, with necessary actions, the suicide of a person. 3. If the cooperation should reach the point of executing death, it will be punished with a 6 to 10 year prison sentence. 4. Anyone causing or actively cooperating in, with necessary actions, in the death of another person, following a serious and express request of this person, in the event that the victim suffers a serious disease that would necessarily lead to his or her death, or that would produce serious permanent suffering difficult to support, will be punished with a sentence that is one or two degrees less than those indicated in nos. 2 and 3 of this article.	*Penalised:* Inducing suicide, simple cooperation and cooperation that leads to executing the death. *Not punishable:* Omissions of help or treatment that are not subject to being qualified as cause or as active cooperation, so long as two requirements intervene: *objective* —disease— and *subjective* —patient's request—. *The Criminal Code:* 1. De-categorises the so-called «passive and indirect» euthanasia, as it requires active and direct behaviours. 2. Categorises «active» euthanasia, but in a very reduced manner. 3. It reduces the sentence for consented homicide with respect to the simple homicide of article 138.

In Recommendation 1418 of the Parliamentary Assembly of the Council of Europe, adopted on 25 June 1999: The Assembly calls upon member states to provide in domestic law the legal and social protection against these specific dangers and fears which a terminally ill or dying person may be faced with, and in particular against:

1. Dying exposed to unbearable symptoms (pain, dyspnoea, etc.).
2. Prolongation of the dying process of a terminally ill person against his or her will.
3. Dying alone and neglected.
4. Dying under the fear of being a social burden.
5. Limitation of self-sustaining treatment due to economic reasons.
6. Insufficient provision of funds and resources for adequate supportive care of the terminally ill or dying persons.

Use of medications in different conditions of use to those authorised

In Spain, both Royal Decree 223/2004, whereby clinical trials on medications are regulated, and Law 29/2006, on Guarantees and Rational Use of Medications, establish that a medication can be used in different indications or conditions for use to those only approved within a clinical trial or as compassionate use. ***Compassionate use*** is understood as the «use in isolated patients and outside a clinical trial, of products in clinical research phase, or also the use of medications for different indications or conditions for use to those authorised, when the physician, under his or her exclusive responsibility, considers its use essential». To use a medication under compassionate conditions for use the informed written consent of the patient or his or her legal representative is required, as well as a clinical report where the physician justifies the need for this treatment, the agreement of the director of the centre where the treatment is going to be applied and the authorisation of the Directorate General for Pharmacy and Health products for each specific case.

However, processing via the compassionate use channel is not always the most satisfactory for certain situations, as often occurs in palliative care; therefore, as development to the Law on Guarantees and Rational Use of Medication, the Spanish Medication Agency is currently developing a Ministerial Order to facilitate access to medications submitted to special conditions.

Appendix 5. Handbook

Handbook by symptoms

Symptom	Drug	Recommended dose	Remarks
PAIN *See appendix on opioids	**PARACETAMOL**	OR: 500-1000 mg/4-6 h (max 4 g/day) Rectal: 650 mg/4-6 h IV: 1000 mg/6 h Maximum dose: 4 g/day	
	METAMIZOL (dypirone)	OR: 500-2000 mg/6-8 h Rectal: 1000 mg/6-8 h IV-IM: 2000 mg/6-8 h	• Risk of agranulocytis and aplastic anaemia
	IBUPROFEN	OR: 400-600 mg/6-8 h Rectal: 500 mg/8 h Maximum dose: 2400 mg/day	• Adjust dose in the elderly and renal insufficiency • It use is admitted in patients who take oral anticoagulants • The NSAIA are the first option in bone pain
	DICLOFENAC	OR: 50 mg/8 h OR retard: 75-150 mg/24 h Rectal: 100 mg/24 h IM-IV: 75 mg/24 h (exceptionally 150 mg/24 h) Maximum dose: 150 mg/day	• Adjust dose in the elderly and renal insufficiency • It use is admitted in patients who take oral anticoagulants • The NSAIA are the first option in bone pain • It can be used in SC continuous infusion (not in bolus), but do not mix with other drugs*
	NAPROXEN	OR or rectal: 500 mg/12 h	• Adjust dose in the elderly and renal insufficiency
	KETOROLAC	OR: 10 mg/6-8 h IV-IM-SC: 10-30 mg/6-8 h Maximum dose: 40 mg/day	• Adjust dose in the elderly and renal insufficiency • It use is admitted in patients who take oral anticoagulants • The NSAIA are the first option in bone pain • Greater risk of haemorrhage than other NSAIA • Drug for hospital use • It can be used by SC route, but do not mix with other drugs”
	CODEINA	OR: 30-60 mg/4-6 h Maximum dose: 180-240 mg/day	• It may be necessary to associate laxative • Available in syrup
	PARACETAMOL + CODEINE	OR: 500-650/30 mg 1-2 tab./6 h Maximum dose: 4 g of paracetamol	• It may be necessary to associate laxative • There is a presentation in syrup but with low doses

Symptom	Drug	Recommended dose	Remarks
PAIN *See appendix on opioids	**DIHYDROCODEINE**	OR: 30 mg/4-6 h	• Not marketed in Spain in tablets or phials, available only in syrup or drops, at low doses • It may be necessary to associate laxative
	TRAMADOL	OR: 50-100 mg/6-8 h OR retard: 100-200 mg/12 h Rectal: 100 mg/6-8 h SC-IM: 50-100 mg/ 6-8 h Maximum dose: 400 mg/day	• It may be necessary to associate laxative • Reduce dose in the elderly and renal insufficiency • Less drowsiness and constipation than codeine, but greater risk of interactions (SSRI, tricyclic antidepressants, triptans, MAOI, oral anticoagulants, bupropion, neuroleptics) • It can be administered SC route
	PARACEMATOL+ TRAMADOL	OR: 650/75 mg/6-8 h (2 tab./6-8 h) Maximum dose: 8 tab./day	See TRAMADOL
	MORPHINE*	OR: 10-30 mg/ 4 h Retard method:10-30 mg/12 h SC-IM route: half the dose of OR Dose increases: 25-50% of dose Double the dose can be given at bedtime to prevent one dose	• It has no therapeutic ceiling except for the appearance of adverse effects • Associate laxative • Antidote: Naloxone • It can be administered by SC route
	ORAL SOLUTION MORPHINE*	Irruptive pain or as rescue: 1/6 of the total daily dose	• Irruptive pain and as rescue • Adequate if swallowing problems
	FENTANYL*	Initial dose in patients not treated with opioids: 25 mcg/h match every 72 h, increase the dose by 12-25 mcg/h every 72 h until efficient dose Treated with morphine: according to morphine dose *	• The increase in temperature increases its absorption • Associate laxative • Rescue: with rapid release oral morphine or oral transmucosal fentanyl • Useful in rotation with opioids
	ORAL TRANSMUCOSAL FENTANYL	0.2-1.6 mg on demand The dose cannot be predicted based on the maintenance dose	• Irruptive pain and as rescue • Quick and short action (15 minutes-4 hours)
	METHADONE*	OR, SC, IM: initial dose: 5-10 mg/6-8 h adapted according to response If used for a long time do not administer with time intervals of less than 12 h	• Long average life with risk of accumulation • Renal and hepatic insufficiency do not interfere in its elimination • Wide inter-individual variability in dose • Handling by expert personnel • Useful in rotation of opioids • Associate laxative • It can be administered by SC route

Symptom	Drug	Recommended dose	Remarks
PAIN *See appendix on opioids	**OXYCODONE***	OR: initial dose: 10 mg/12 h	• Adjust dose in renal and hepatic insufficiency • Associate laxative
	RAPID OXYCODONE*	OR: 4.5-18 mg on demand	• Irruptive pain and as rescue
	BUPRENORFIN*	Transdermal: initial dose: one 35 µg/h match every 72 h. In patients treated previously with morphine: according to morphine dose SL: 0,2 mg/8 h IV-IM: 0,3-0,6 mg/6-8 h	• The patches can be cut to adapt the dose to each patient • It does not require narcotics prescription
NEUROPATHIC PAIN	**AMITRIPTYLINE**	Initial dose: 10-25 mg/day in single dose at night Normal dose: 50-150 mg/day Maximum dose: 150 mg/day	• Precaution in patients with arrhythmia or ischemic cardiopathy • The treatment must be withdrawn gradually
	DULOXETIN	Initial dose: 60 mg/day in single dose Normal dose: 60 mg/day Maximum dose: 120 mg/day in divided doses	• Approved in technical data sheet for diabetic neuropathy • The treatment must be withdrawn gradually
	CARBAMAZEPINE	Initial dose: 100-200 mg/12 h Increase by 100-200 mg every week Normal dose: 600-800 mg/day in 3 or 4 doses Maximum dose: 1.600 mg	• Precaution in hepatic insufficiency • Requires haematological surveillance • Multiple interactions
	GABAPENTIN	Initial dose: 300 mg 1st day, 300 mg/12 h 2nd day, 300 mg/8 h 3rd day Increase doses at a rate of 300 mg/day Normal dose: 1200-1400 mg/day (2 or 3 doses) Maximum dose: 3.600 mg/day	• Reduce the dose in renal insufficiency and the elderly
	PREGABALIN	Initial dose: 50-150 mg/day in 2-3 doses. Increase by 50-150 mg every week Normal dose: 300-600 mg/day Maximum dose: 600 mg/day	• Reduce the dose in renal insufficiency and the elderly
	MORPHINE	Initial dose: 5-15 mg rapid release every 4 hours. After 7-15 days changed to retarded release Normal dose: 120 mg/day	See PAIN section

Symptom	Drug	Recommended dose	Remarks
NEUROPATHIC PAIN	**TRAMADOL**	Initial dose: 50 mg/day in 2 doses. Increase by 50 mg every week Normal dose: 50-100 mg/6-8 h	• See PAIN section
BONE PAIN	**PAMIDRONIC ACID**	IV perfusion: 90 mg in 250 ml in 2 h every 3-4 weeks In patients with multiple myeloma do not exceed 90 mg in 500 ml for 4 h	• Precaution in cardiopathies and renal insufficiency • Maxillary osteonecrosis has been described (dental revision is recommended prior to treatment) • Duration of treatment more than 6 months • It must not be administered in bolus • Hospital use
	ZOLEDRONIC ACID	IV perfusion: 4 mg/100 ml in 15 minutes at least, every 3-4 weeks	• Precaution in cardiopathies and renal insufficiency • Maxillary osteonecrosis has been described (dental revision is recommended prior to treatment) • Duration of treatment more than 6 months • Hospital use
MYCLONUS BY OPIOIDS	**MIDAZOLAM**	OR, IV, SC: 5-10 mg	• It can be used by SC route* • Ampoules of Hospital use
	BACLOPHEN	Initial dose OR: 5 mg/8 h Normal dose OR: 10-15 mg/8 h Maximum dose: 100 mg/day	• Progressive withdrawal due to risk of abstinence
	CLONAZEPAM	OR: initial dose 0,5-1,5 mg/day, normal dose 3-6 mg/day, maximum dose: 20 mg/day IV: 1 mg in slow IV injection (2 minutes) or slow IV perfusion	• Reduce dose of opioids or rotation • It can be used by SC route*
	DIAZEPAM	OR, rectal or IV: 5-10 mg	
ASTHENIA	**PREDNISONE**	OR: 20-40 mg/day	• Its effect is temporary (2-4 weeks) so it is recommended in patients with life expectation < 4 weeks • In short series (up to 3 weeks) it is normally necessary to withdraw it gradually
ANOREXIA AND CACHEXIA	**ACETATE MEGESTROL**	OR initial dose: 160 mg/day OR normal dose: 320-800 mg/day Maximum dose: 800 mg/day	• Its effect takes weeks to disappear so it is recommended in patients with life expectation 2-3 months
	DEXAMETASONE	OR: 3-8 mg/day (dose used in clinical trials	• It can be used by SC route, but it is not recommended to mix with other drugs in SC infusion* • Corticosteroids have been used in 1-8 week patterns. In short series (up to 3 weeks) gradual withdrawal is not normally necessary

Symptom	Drug	Recommended dose	Remarks
ANOREXIA AND CACHESIA	PREDNISOLONE	OR: 10 mg/day (dose used in clinical trials) Dose range: 10-30 mg/day	• Corticosteroids have been used in 1-8 week series. In short series (up to 3 weeks) gradual withdrawal is not normally necessary
	METHYLPREDNISOLONE	OR: 32 mg/day IV: 125 mg/day (dose used in clinical trials)	• It can be administered by SC route* • Corticosteroids have been used in 1-8 week series. In short series (up to 3 weeks) gradual withdrawal is not normally necessary
	CIPROHEPTADINE	OR: 45 mg/8 h	• Further studies are required on its efficiency
	METHYLFENIDATE	OR: 5-15 mg/day	• Further studies are required on its efficiency • Contraindications: angina, arrhythmias or serious HBP, serious depression, psychotic symptoms, suicide tendencies • Administer in the morning or at midday due to possible insomnia effect
	MODAFINIL	OR: 200-400 mg/day	• Further studies are required on its efficiency, little experience of use • Contraindicated in serious anxiety • Precaution in renal and hepatic insufficiency, cardiovascular disturbances, depression, mania and psychosis
DYSPNOEA	MORPHINE	If not being treated with morphine: OR, SC: 2.5-5 mg/4 h If being treated with morphine: increase dose by 25-50%	• Associate laxative • Antidote: Naloxone • It can be administered by SC route
	OXYCODONE	OR: 2.5-5 mg/4 h	• Associate laxative
	PROMETAZIN	OR, IM, IV: 25 mg/8-12 h or on demand	• As an adjuvant or second line drug, opioids cannot be administered or associated with them
	LORAZEPAM	OR: 0.5-1 mg on demand or in series	• Dyspnoea associated with anxiety
	ALPROZOLAM	OR: 0.25-0.5 mg on demand or in series 0.25-0.5/8 mg/h	• Dyspnoea associated with anxiety • Quick action and short duration
	MIDAZOLAM	OR: 7.5 mg on demand or in series 7.5 mg/8 h	• Dyspnoea associated with anxiety • It can be used by SC route* • Quick action and short duration • Ampoules for hospital use

Symptom	Drug	Recommended dose	Remarks
DYSPNOEA	DIAZEPAM	OR: 5 mg on demand or in series 5-20 mg/day on 1-2 doses	• Dyspnoea associated with anxiety • Longer action
	DIPOTASSIUM CLORAZEPATE	OR: 5-10 mg on demand or in series 7.5-25 mg/day in 2-3 doses.	• Dyspnoea associated with anxiety • Longer action
	CLORPROMAZIN	OR: 7.5-25 mg/6-8 h or on demand	• IM route may be painful • As adjuvant or second line drug, opioids cannot be administered or associated with them
	LEVOMEPROMAZIN	OR, SC: 2.5-10 mg	• As adjuvant or second line drug, opioids cannot be administered or associated with them • It can be used by SC route* • (levomepromazin is also known as methotrimeprazin)
	SALBUTAMOL	Inhaled: 1-2 squirts on demand	• Dyspnoea inpatients with reversible obstruction of airway
	PREDNISONE	OR: 20-40 mg/day	• Dyspnoea in patients with asthma, COPD, carcinomatous lymphangitis or obstructive tumours of the airway. • In short series (up to 3 weeks) gradual withdrawal is not normally necessary
COUGH	LEVODROPROPIZIN	OR: 60 mg/8 h	• No opioid
	CLOPERASTIN	OR: 10-20 mg/8 h	• No opioid
	CODEINE	OR: 10-20 mg/4-6 h	• Associate laxative
	DIHYDROCODEINE	OR: 5-10 mg/4-6 h Maximum dose: 120 mg/day	• Not marketed in Spain in tablets or phials, available only in syrup and drops
	MORPHINE	OR: 2,5-5 mg/4-6 h	• Associated laxative • Antidote: Naloxone • It can be administered by SC route
	DEXTROMETORPHANE	OR: 10-20 mg/4-6 h o 30 mg/8 h Maximum dose: 120 mg/day	• Precaution in hepatic insufficiency • Some presentations cannot be financed
	DISODIUM CROMOGLICATE	20 mg/6 h inhaled	• In case of failure of previous treatments in lung cancer

Symptom	Drug	Recommended dose	Remarks
COUGH	BUPIVACAINE	5 ml/6-8 h sprayed	• Premedicate with bronchodilators (salbutamol) • Risk of aspiration after application so no intake is recommended until 1 hours later • Resistant cough, in very selected cases
	LIDOCAINE	5 ml/6-8 h sprayed	• Premedicate with bronchodilators (salbutamol) • Risk of aspiration after application so no intake is recommended until 1 hours later
DELIRIUM	HALOPERIDOL	Range of normal dose OR, SC, IM, IV: 0.5-5 mg/2-12 h Normal dose OR: 1-3 mg/8 h Normal dose SC bolus: 2.5 mg (every 30 minutes, Maximum 3 times) Normal dose SC infusion: 5-15 mg/day	• Of choice in delirium • Greater risk of extra-pyramidal symptoms if associated with other neuroleptics and metoclopramide • Low sedative profile • It can be used by SC route*
	LEVOMEPROMAZINE	Range of normal dose OR, SC, IM: 12,5-50 mg/4-12 h Normal dose SC bolus: 12,5 mg (every 30 minutes, Maximum 3 times) Normal dose in SC infusion SC: 50-200 mg/day	• More sedative than haloperidol, alternative to haloperidol in patient with delirium with intense anxiety • It can be used by SC route*
	MIDAZOLAM	SC, IV bolus: 2.5-5 mg and repeat until it stops. Maintenance in IV perfusion, SC: 20-100 mg/day Maximum dose: 200 mg/day	• Alternative to haloperidol and levomepromazine in delirium with intense anxiety • It can be used by SC route* • Ampoules of Hospital Use
INSOMNIA	ZOLPIDEM	OR: 5-10 mg at bedtime	• Quick action and short duration • Precaution in serious hepatopathy • Conciliation insomnia
	ZOPICLONE	OR: 7.5 mg at bedtime	• Quick action and short duration • Conciliation insomnia • Precaution in serious hepatopathy
	LORAZEPAM	OR: 0,5-2 mg at bedtime	• Intermediate duration. Sleep induction and maintenance. Little daytime sedation.

Symptom	Drug	Recommended dose	Remarks
INSOMNIA	LORMETAZEPAM	OR: 0,5-2 mg at bedtime	• Intermediate duration. Sleep induction and maintenance. Little daytime sedation
	CLOMETIAZOL	OR: 192 mg at bedtime	• It can be useful to avoid delirium
	DIAZEPAM	OR: 5.-10 mg at bedtime	• Daytime maintenance and anxiety • Available by rectal route
	TRAZODONE	OR: 25-100 mg at bedtime	• Insomnia associated with depression
	MIRTAZAPIN	OR: 15-30 mg at bedtime	• Insomnia associated with depression and/or anorexia
	AMITRIPTYLINE	OR: 25-100 mg at bedtime	• Precaution in patients with arrhythmia or ischemic cardiopathy • In insomnia associated with depression or neuropathic pain
ANXIETY	LORAZEPAM	OR 1-2 mg/8-12 h or 2 mg on demand	• Quick action and intermediate duration
	ALPRAZOLAM	OR: 0.25-0.5 mg/8 h or on demand	• Quick action and intermediate duration • Useful in anxiety crisis
	MIDAZOLAM	OR: 7.5 mg/8 h or 7.5 mg on demand	• Quick action and short duration • It can be used by SC route* • Ampoules of Hospital use
	DIAZEPAM	OR: 5-20 mg/day in several doses or 5 mg on demand	• Longer action • Available by rectal route
	DIPOTASSIUM CLORAZEPATE	OR: 5-10 mg/12 h or on demand	• Quick start of action, prolonged duration
	CLONAZEPAM	OR: 4-8 mg/day in 3 or 4 doses or 0.5-1 mg on demand	• It can be used by SC route*
	CLOMETIAZOL	OR: 192 mg/8 h or on demand	• It can be used to avoid delirium
	HALOPERIDOL	OR: 1,5-5 mg on demand or in series 3-10 g/8 h	• It can be used by SC route* • Greater risk of extra-pyramid symptoms if associated with drugs such as metoclopramide • Anxiety accompanied with hallucinations or delirium
	LEVOMEPROMAZINE	OR: 25-75 mg/day in 2-3 doses	• It can be used by SC route* • Anxiety accompanied with hallucinations or delirium

Symptom	Drug	Recommended dose	Remarks
DEPRESSION	MIANSERIN	OR: 20-60 mg/day	• In one or several daily doses • Minimum anticholinergic effects • Precaution in patients with diabetes mellitus, epilepsy and hepatic or renal insufficiency
	FLUOXETINE	OR: normal dose 20 mg/day	• Start with low doses in the elderly (10 mg) • Adverse effects at C.N.S. level (agitation, cephalalgia, insomnia, etc.) • Precaution in diabetics, renal insufficiency and epileptics
	PAROXETINE	OR: normal dose 20 mg/day	• More sedative than fluoxetine • Do not suspend treatment suddenly
	SERTRALINE	OR: 50-100 mg/day	• More sedative than fluoxetine, less risk of interactions • Contraindicated in epileptic patients, renal or hepatic insufficiency
	CITALOPRAM	OR: normal dose 20 mg/day	• Low sedative profile. Less risk of interactions
	AMITRIPTYLINE	OR: 50-100 mg/day	• Maintenance: one dose at bedtime • Adverse anticholinergic, cardiovascular effects, drowsiness and weight gain • Precaution in patients with cardiovascular disturbances, hepatic and renal insufficiency
	TRAZODONE	OR: 100-300 mg Maximum dose: 400 mg/day, elderly 200 mg/day	• It is administered at night (sedative effect) • Less anticholinergic, cardiovascular and extrapyramidal effects • Precaution in administration with azole antifungals, other SSRIs, macrolides
	ALPRAZOLAM	OR: 0.5-4 mg/day Maximum dose: 4 mg/day	• Quick action and short duration • It is a benzodiazepine
	METHYLFENIDATE	OR: 5-30 mg/day	• Little evidence • Contraindications: angina, arrhythmias or serious HBP, psychotic symptoms, suicide tendencies • Effect in 1-2 days so it would be indicated when start of quick action is required or patients with very short life expectation; not recommended in serious depression

Symptom	Drug	Recommended dose	Remarks
MUCOSITIS	BENZYDAMINE	Mouthwashes 15 ml/6 h or in tablets	• Available as mouthwash or in external use tablets • Not fundable
	POVIDONE IODINE	Mouthwashes 10 ml/8-12 h	• Not fundable
	PALIFERMIN	In patients with haematological neoplasia submitted to myeloablative treatment: IV: 60 mcg/kg/day, 3 days before and 3 after myeloablative treatment	• Medication for Hospital Use
XEROSTOMY	PILOCARPIN	OR: 5-10 mg/8 h in tablets	• Precaution: asthma and COPD, cardiovascular disease, cognitive or psychiatric disturbances • Mouthwashes can be used by oral route (4-6 drops/8 h dissolved in fruit juice)
CANDIDIASIS PROPHYLAXIS	ITRACONAZOLE	OR: 100 mg/12 h	• Precaution in hepatopathy
	KETOCONAZOLE	OR: 400 mg/day	• Precaution in hepatopathy
	FLUCONAZOLE	OR: 50 mg/12 h	• Precaution in hepatopathy
DYSPHAGIA	DEXAMETHASONE	OR, SC, IV: 4-8 mg/day	• It can be administered by SC route* • There is an inflammatory component
NAUSEA AND VOMITING	DEXAMETHASONE	Unrelated to chemotherapy: OR, SC, IV: 4-16 mg/day Normal dose used in studies for prevention in chemotherapy, IV: 20 mg/day	• It can be administered by SC route* • Nausea and vomiting due to chemotherapy (moderate-high risk of emesis) and associated to endocranial hypertension • In short series (up to 3 weeks) gradual withdrawal is not usually necessary
	METOCLOPRAMIDE	Normal dose OR, SC, IM, IV: 15-60 mg/day on 2-4 doses SC infusion: 30-100 mg/day Nausea and vomiting related to chemotherapy (parenteral route): 40-60 mg/day	• It can be used by SC route* • Contraindicated in intestinal obstruction • Risks of arrhythmia is associated with ondansetron • Administer 30 minutes before the meals • Contraindicated in patients with Parkinson's disease
	DOMPERIDONE	OR: 10-20 mg/6-8 h Rectal route: 60 mg/8 h	• Administer 15-20 minutes before meals • Extrapyramidal effects are rare

Symptom	Drug	Recommended dose	Remarks
NAUSEA AND VOMITING	ONDANSETRON*	OR, SC, IV: 12-24 mg/day Route and dose variable according to risk of emesis	• Prevention and treatment of nausea and vomiting induced by chemotherapy or radiation therapy • Risk of arrhythmia if associated with metoclopramide • It can be administered by SC route* • Tablets: hospital diagnosis medication, ampoules for Hospital Use
	APREPITANT	OR: 125 mg the 1st day and 80 mg/day the 2nd and 3rd days	• It must be associated with dexametasone and ondansetron • Nausea and vomiting associated with highly emetogenic chemotherapy • Medication for Hospital Use
	HALOPERIDOL	OR, SC, IV:1.5-5 mg/day	• Nausea and vomiting associated with opioids, renal insufficiency or hypercalcaemia • It can be administered by SC route* • Greater risk of extrapyramidal symptoms if associated with metoclopramide or neuroleptics
	CHLORPROMAZINE	OR, IV: 25-50 mg/6-8 h	
	DIMENHYDRATE	OR, rectal: 50-100 mg/4-6 h	• Nausea and vomiting of vestibular origin • Not fundable
	TIETILPERAZINE	OR, rectal: 6,5 mg/8-24 h	• Nausea and vomiting of vestibular origin
	ALPRAZOLAM	OR: 0.5-2 mg/day	• Anticipatory vomiting together with antiemetics
	LORAZEPAM	OR: 2-4 mg/day	• Anticipatory vomiting together with antiemetics
CONSTIPATION	LACTULOSE	Treatment of chronic constipation: initially 15 ml (10 mg)/12 h, as from 2-3 days: 15-30 ml/day Constipation prevention: 15 ml (10 mg)/8-24 h	• May take up to 3 days to have effect • Osmotic laxative • Side effects: cramps and flatulence
	SEN (Cassia angustifolia)	OR: 7.5 mg/8-24 h	• Do not administer if intestinal obstruction • Stimulant laxative • Not fundable
	SENOSIDES A and B	OR: 12-36 mg/24 h	• Do not administer if intestinal obstruction • Stimulant laxative • Not fundable

*** INFORMATION NOTE Spanish Agency of Medicines and Medical Devices (10th August 2012):**
Due the potential risk of arrhytmias, there are new recommendations for the use of ondansetron. The maximum single intravenous dose of ondansetron for chemotherapy induced nausea and vomiting is 16 mg. More information available at:
http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_14-2012.htm (NOTE: website in spanish)

Symptom	Drug	Recommended dose	Remarks
CONSTIPATION	POLYETHYLENGLYCOL	OR: 1 sachet/8-24 h	• Osmotic laxative • Non fundable
	GLYCERINE	Rectal route: 1 suppository/24 h	• In faecal impaction • Non fundable
	PHOSPHATES	Rectal route: 1-2 enemas according to response	• In faecal impaction • Non fundable
	SODIUM PICOSULPHATE	OR: 5-10 mg at night	• Do not administer if intestinal obstruction • Stimulant laxative • Non fundable
	ISPAGHULA (ovate plantain)	OR: 3.5-10 g/day	• Maintain good hydration to avoid obstruction • Mass-forming laxative • Non fundable
	METHYLCELLULOSE	OR: 1500 mg/24 h	• Maintain good hydration to avoid obstruction • Mass-forming laxative • Non fundable
	LIQUID PARAFFIN	OR: 15 ml/12-24 h	• Lubricant laxative • Non fundable
	BISACODYL	OR: 5-10 mg at bedtime Rectal route: 1 suppository/day	• Lubricant laxative • Non fundable
	MAGNESIUM SALTS	OR: 2.4-3.6 g/day	• Risk of hypomagnesaemia in renal insufficiency • Osmotic laxative • Non fundable
DIARRHOEA	LOPERAMIDE	OR: Initial dose 4 mg and followed by 2 mg after each bowel movement up to a maximum of 16 mg/day	• Risk of paralytic ileus
	OCTREOTIDE	SC: 50-500 µg/day Maximum dose: 1.500 µg/day	• Refractory diarrhoea • It can be administered by SC route • Hospital diagnosis medication (indication not included in technical data sheet)
	CODEINE	OR: 30 mg/6 h	

Symptom	Drug	Recommended dose	Remarks
INTESTINAL OBSTRUCTION	OCTREOTIDE	SC: 300-800 µg/day SC infusion: 300-600 µg/day Maximum dose: 1.500 µg/day	• It can be administered by SC route • Refractory diarrhoea • Hospital diagnosis medication (indication not included in technical data sheet)
	BUTYLSCOPLAMINE	IV, SC: 60-80 mg/day in 3-4 doses SC infusion: 60-80 mg/day	• It can be administered by SC route. Also called scopolamine butyl bromide • Do not confuse the dose with that of scopolamine bromhydrate (not marketed in Spain)
	DEXAMETASONE	IV, SC route: 4-16 mg/day	• It can be administered by SC route* • Do not mix with other drugs in SC infusion
ASCITES	FUROSEMIDE	OR, IM, IV, SC: 40-80 mg/day	• Risk of dehydration and hypopotasemia • It can be administered by SC route*
	SPIRONOLACTONE	OR. 100/400 mg/day	• Risk is dehydration and hyperpotasemia
HICCUPS	BACLOFEN	OR: 5-20 mg/8 h	• Progressive reduction due to risk of abstinence
	NIFEDIPINE	OR: 10-20 mg/8 h	• It can produce hypotension, above all by SL route
	OMEPRAZOL	OR: 20 mg/day	
	METOCLOPRAMIDE	OR, IV, SC: 10 mg/6-8 h	• Contraindicated in intestinal obstruction • Risk of arrhythmia if associated with ondansetron • It can be administered by SC route*
	CHLORPROMAZINE	OR, IM: 25 mg/6-8 h	• IM route can be painful
	GABAPENTIN	OR: 300-600 mg/8 h	• Maximum dose: 3600 mg/day
	HALOPERIDOL	OR: 3 mg at night	• It can be administered by SC route* • Greater risk of extrapyramidal symptoms if associated with other drugs such as metoclopramide
	MIDAZOLAM	5-10 mg bolus IV-SC and continue with SC perfusion of 30-60 mg/day	• It can be administered by SC route* • If certain sedation is acceptable to control symptoms • Ampoules of Hospital use
FUNGATING WOUND	MILTEFOSINE	External use: 1-2 applications/day	• Medication of hospital diagnosis
	METRONIDAZOLE	External use: 1 application/8 h	

Symptom	Drug	Recommended dose	Remarks
PRURITUS	NALTREXONE	OR: Onset 12.5/12 h increase to maintenance dose of 50-300 mg/day	• Cholestasis-induced pruritus • It antagonises the effects of opioids with risk of deprivation
	DANAZOL	OR: 100 mg/1-3 times a day	• Cholestasis-induced pruritus
	RIFAMPICINE	OR: 300-600 mg/8-12 h	• Cholestasis-induced pruritus • It stains urine, saliva and other body fluids orange
	CHOLESTYRAMINE	OR: 4 g/8 h	• Cholestasis-induced pruritus • Limited digestive tolerance
	CIMETIDINE	OR: 400 mg/12 h	• Pruritus associated with haematological neoplasias
	ONDANSETRON	OR, SC: 4-8 mg/8 h	• Uraemia and opioid-induced pruritus • Risk of arrhythmia is associated with metoclopramide • It can be administered by SC route • Tablets: hospital diagnosis, phials: Hospital Use (indication not included in technical data sheet)
	DEXCLORFENIRAMINE	OR: 2 mg/6-8 h IV: 5 mg/6-8 h	• Uraemia-induced and dry skin pruritus • It produces sedation
	HYDROXICINE	OR: 25 mg/8-24 h	• Uraemia-induced and dry skin pruritus • It produces sedation
	LORATADINE	OR: 10 mg/day	• Uraemia-induced and dry skin pruritus • Low incidence of sedation and muscarinic effects (urinary retention, dryness of mouth, blurred vision
	PAROXETINE	OR: 20 mg/day Start with low doses in the elderly (10 mg)	• Pruritus due to haematological neoplasias or paraneoplastic • One single dose a day (mornings) • It takes weeks to have effect
	MIRTAZAPINE	OR: 7.5-15 mg/day	• Uraemia-induced or paraneoplastic pruritus • Presentation of oral dispersible tablets
URINARY URGENCY	OXYBUTYNIN	OR: 2.5-5 mg/6-12 h	• Anticholinergic adverse effects
	TOLTERODIN	OR: 2 mg/12 h	• Anticholinergic adverse effects
	TROSPIUM CHLORIDE	OR: 20 mg/12 h	• Anticholinergic adverse effects

Symptom	Drug	Recommended dose	Remarks
URINARY URGENCY	IMIPRAMINE	OR: 25-50 mg/day	• Precaution in patients with arrhythmia or ischemic cardiopathy
	AMITRIPTYLINE	OR: 25-50 mg at night	• Precaution in patients with arrhythmia or ischemic cardiopathy
	BUTYLSCOPOLAMINE	OR, IV, SC: 20-30 mg/6-8 h	• It can be administered by SC route • Presented in suppositories • Also called scopolamine butylbromide (do not confuse with scopolamine bromhydrate)
	IBUPROFEN	OR: 400-600 mg/8 h Rectal: 500 mg/8 h	• Adjust dose in elderly and renal insufficiency
	NAPROXEN	OR, rectal: 500 mg/12 h	• Adjust dose in elderly and renal insufficiency
HYPERCALCEMIA	PAMIDRONIC ACID	IV perfusion: 30-90 mg in 2-4 h (do not exceed 90 mg in 500 ml for 4 hours)	• Precaution in cardiopathies and renal insufficiency • Maintain good hydration • The dose depends on levels of serum calcium • Maxillary osteonecrosis has been described (dental revision is recommended prior to treatment) • Hospital use
	ZOLEDRONIC ACID	IV perfusion: 4 mg in 15 minutes minimum (diluted with 100 ml sodium chloride at 0.9% or glucosate 5%)	• Precaution in cardiopathies and renal insufficiency • Maintain good hydration • Maxillary osteonecrosis has been described (dental revision is recommended prior to treatment) • Hospital use
	IBANDRONIC ACID	IV perfusion: 2-4 mg in 15 minutes minimum (diluted with 100 ml sodium chloride at 0.9% or glucosate	• Maintain good hydration • Hospital use
	CALCITONIN	IM, SC: 4-8 UI/kg/12 h	• Intranasal route is not efficient • It can be administered by SC route
	PREDNISOLONE	OR: 40-100 mg/day	
SPINAL CORD COMPRESSION	DEXAMETHASONE	Initial IV bolus: 10-100 mg, following by dose of 16 mg/day OR. (doses used in clinical trials)	• It can be administered by SC route* • Associated with radiation therapy • The initial dose of 100 mg was associated with more serious adverse effects than the 10 mg dose, although it was more efficient • Treatments lasting for less than 3 weeks generally do not require gradual withdrawal

Symptom	Drug	Recommended dose	Remarks
SEIZURES	DIAZEPAM	IV, rectal: 5-10 mg IV infusion: 2,5-5 mg/minute	• Treatment of acute crisis
	MIDAZOLAM	IV, SC: 10-15 mg	• It can be administered by SC route* • Treatment of acute crisis
	SODIUM VALPROATE	OR: 20-30 mg/kg/day distributed into 2-3 doses	• Secondary prevention of convulsive crisis • Contraindicated in hepatopathy
	FENITOINE	OR 4-8 mg/kg/day distributed into 3 doses. Normal dose: 100 mg/8 h Maximum dose: 600 mg/day	• Secondary prevention of convulsive crisis • Narrow therapeutic margin • It can induce numerous interactions
	FENOBARBITAL	OR: 60- 250 mg/day distributed into 2 doses	• It can be administered by SC route • Secondary prevention of convulsive crisis • Drowsiness, hyperkinesias in children, confusion in elderly
	CARBAMAZEPIN	OR: 200-400 mg/8-12 h	• Precaution in hepatic insufficiency • Requires haematological surveillance • Secondary prevention of convulsive crisis
	CLONAZEPAM	OR: 3-6 mg/day distributed into 3 doses	• Secondary prevention of convulsive crisis • It can be administered by SC route*
	GABAPENTIN	OR: 100-400 mg/8 h Maximum dose: 3.600 mg/day	• Secondary prevention of convulsive crisis
	LAMOTRIGINE	OR: 100-200 mg/day distributed into 2 doses	• Secondary prevention of convulsive crisis
	TOPIRAMATE	OR: 100-200 mg/12 h	• Secondary prevention of convulsive crisis
BLEDDING	AMINOCAPROIC ACID	IV perfusion: 4 g in first four and then 1 g/h Oral route: 4 g/6 h	• Contraindicated in serious renal insufficiency • Drunk ampoules have been used for oral administration
	TRANEXAMIC ACID	OR: 1-1,5 g/8-12 h IV, IM: 0.5-1 g/8-12 h	• Contraindicated in serious renal insufficiency • Tablets or drunk ampoules can be used for oral administration

Symptom	Drug	Recommended dose	Remarks
SEDATION	MIDAZOLAM	**SC route sedation:** *Induction:* 2.5-5 mg *Perfusion:* 0.4-0.8 mg/h *Rescue:* bolus 2.5-5 mg Double dose if benzodiazepine taken previously **IV route sedation:** *Induction:* 1.5-3 mg every 5 min until sedated (the required dose will be the induction dose) *Perfusion:* induction dose x 6 *Rescue:* induction dose	• Double the sedation dose if the patient was already taking benzodiazepines • Maximum dose: 200 mg/day • It can be administered by SC route* • Ampoules of Hospital Use
	LEVOMEPROMAZINE	**SC route sedation:** *Induction:* 12.5-25 mg *Perfusion:* 100 mg/day *Rescue:* 12.5 mg **IV route sedation**: Half the dose used by SC route	• Sedation when the prevailing symptom is delirium • Maximum dose: 300 mg. • It can be administered by SC route*
	PROPOFOL	**IV sedation** *Induction:* 1-1,5 mg/kg *Perfusion:* 2 mg/kg/h *Rescue:* bolus of 50% the induction dose	• Previously suspend BZD perfusion or neuroleptics and reduce opioids to half • Hospital Use
	FENOBARBITAL	**SC route sedation:** *Induction:* 100-200 mg *Perfusion:* 600 mg/day *Rescue:* bolus 100 mg **IV route sedation:** *Induction:* 2 mg/kg slow *Perfusion:* 1 mg/kg/h and modify according to response	• Previously suspend BZD perfusion or neuroleptics and reduce opioids to half • Indicated if midazolam and levomepromazine fail • It can be administered by SC route
PREMORTEM DEATH RATTLES	BUTYLSCOPOLAMINE	IV, SC: 20 mg/4-6 h or Perfusion of 20-100 mg/day	• Also called scopolamine butylbromide • Do not confuse with scopolamine bromhydrate (not marketed in Spain)

OR: oral route. SC: subcutaneous. IV: intravenous. IM: intramuscular. SL: sublingual.
* Use of SC route: not included in technical data sheet.
** Some indications are not included in technical data sheet.

Pharmacological characteristics of the most commonly used corticosteroids

	Average life (h)	Equivalent dose (mg)	Glucocorticoid power (anti-inflammatory)	Mineral-corticosteroid power
Short action				
Cortisone	8-12	25	0.8	0.8
Hydrocortisone	8-12	20	1	1
Intermediate action				
Deflazacort	18-36	7.5	4	0.5
Methylprednisolone	18-36	4	5	0.5
Prednisolone	18-36	5	4	0.8
Prednisone	18-36	5	4	0.8
Triamcinolon	18-36	4	5	0
Long action				
Betamethasone	36-54	0.6-0.75	25-30	0
Dexamethasone	36-54	0.75	25	0
Paramethasone	36-54	2	10	0

Handbook by substance

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
ALPRAZOLAM	Alprazolam GD Grankimazine®	Tab: 0.25-0.5-1-2-3 mg Drops: 0.75 mg/ml	**Anxiety**: 0.25-0.5 mg/8 h or on demand **Dyspnoea with anxiety:** 0.25-0.5 mg on demand or series 0.25-0.5/8 h **Depression**: 0.5-4 mg/day **Anticipatory vomiting**: 0.5-2 mg/ay	Drowsiness, confusion, ataxia, amnesia, dependence, muscular weakness, hypotension, dysarthria, urinary incontinence	Useful in panic crises
AMINOCAPROIC ACID	Ampoules: Capromain fides®	Ampoules: 4 mg	**Haemorrhage:** IV perfusion: 4 g in first hour and then 1 g/h Oral route: 4 g/6 h	Nausea, abdominal pain, diarrhoea, myalgias, weakness rhabdomyolysis with myoglobinuria, thrombosis	Drunk ampoules have been used for oral administration
AMITRIPTYLINE	Tryptizol® Deprelio®	Tab: 10-25-50-75 mg	**Neuropathic pain:** Initial dose: 10-25 mg/day in single dose at night Normal dose: 50-150 mg/day Maximum dose: 150 mg/day **Insomnia associated with depression or neuropathic pain:** 25-100 mg at bedtime **Depression:** 50-100 mg/day **Vesical tenesmus:** 25-50 mg at night	Dry mouth, sedation, urinary retention, orthostatic hypotension, cardiovascular disturbances	Precaution in patients with arrhythmia or ischemic cardiopathy. The treatment must be withdrawn gradually.
APREPITANT	Emend®	Caps: 80-125 mg	**Nausea and vomiting associated with emetogenic chemotherapy:** OR: 125 mg 1st day and 80 mg/day 2nd and 3rd days	Hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, cephalea, dry mouth, flatulence, abdominal pain, ulcers, bradycardia, cough, disorientation, disuria	It must be associated with dexamethasone and ondansetron Hospital use
BACLOFEN	Lioresal®	Tab: 10-25 mg	**Hiccups: 6-20 mg/k h** **Opioid-induced myoclonus** Initial dose: 6 mg/8h Normal dose: 10-15 mg/8h Maximum dose: 100 mg/day	Sedation, drowsiness, muscular hypotonia, nausea, dizziness, speech disorders, insomnia, depression, anxiety, paresthesia, convulsions	Progressive withdrawal due to risk of abstinence
BENZYDAMINE	Tantum Verde®	Pill: 3 mg Mouthwash at 0.15%	**Mucositis**: Mouthwashes 15 ml/6h or in pills	Numbness, itchiness	Not fundable
BISACODYL	Dulco laxo®	Tab: 5 mg Supp: 10 mg	**Constipation:** OR: 5-10 mg at bedtime Rectal route: 1 suppository/day	Abdominal cramp, abdominal distension	Not fundable

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
BUPIVACAINE	Bupivacaina®	Ampoules at 0.25% (25 mg in 10 ml)	**Cough:** 6 ml/6-8 h spray	Risk of aspiration	Resistant cough, in very selected cases
BUPRENORFIN	Prolonged release patches: Transtc® Sublingual tab. And ampoules Buprex®	Patches: 35-52-5-70 µg/h SL Tab: 0.2 mg Ampoules: 0.3 mg	**Pain:** Transdermal: initial dose: one 35 µg/h patch every 72 h. In patients treated previously with morphine: according to morphine dose SL: 0.2 mg/8h IV-IM: 0.3-0.6 mg/6-8 h	Nausea, vomiting, constipation, drowsiness, dry mouth, perspiration, respiratory depression, hallucinations, dysphoria, urinary retention, myoclonus, local rash due to patch	The patches can be cut to adapt dose to each patient. Does not require narcotics prescription
BUTYLSCOPO-LAMINE	Buscapina®	Tab. 10 mg Suppositories: 10 mg Ampoules: 20 mg	**Intestinal obstruction:** IV, SC: 60-80 mg/day in 3-4 doses SC infusion: 60-80 mg/day **Premortem death rattles:** IV, SC: 20 mg/4-6 h or perfusion of 20-100 mg/day **Vesical tenesmus:** OR, IV, SC: 20-30-mg/6-8 h	Dry mouth, blurred vision, tachycardia, hypotension, urinary retention	Do not confuse dose with that of scopolamine bromhydrate (not marketed in Spain, its dosage is different)
CALCITONIN	Calcitonin Almirall® Calogen® Calsynar® Miacalcic®	Phial: 60-10 UI	**Hypercalcaemia:** IM, SC 4-8 UI/kg/12 h	Nausea, vomiting, diarrhoea, abdominal pain, flushing, dizziness, cephalea, myalgias, visual disturbances, local reaction at injection spot	Intranasal route is not efficient. Can be administered by SC route
CARBAMAZEPINE	Carbamazepine DG. Tegretol®	Tab: 200-400 mg	**Neuropathic pain:** Initial dose: 100-200 mg/12 h Increase by 100-200 mg every week Normal dose: 600-800 mg/day in 3 or 4 doses Maximum dose: 1600 mg/day **Secondary prevention of convulsive crises:** 200-400 mg/8-12 h	Drowsiness, dizziness, lack of stability, nausea, skin rash, haematological and hepatic toxicity	Precaution in hepatic failure Requires haematological surveillance
CIMETEDINE	Tagamet® Fremet®	Tab: 200-400-800 mg	**Pruritus in haematological neoplasias:** 400 mg/12 h	Diarrhoea, hepatic function disturbance, cephalea, dizziness, skin rash, bradycardia, AV blockage, pancreatitis, depression, hallucinations	

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
CIPROHEPTADINE	Viternum®	Suspension: 3 mg/ml	**Anorexia/cachexia:** 45 mg/8 h	Nausea, vomiting, constipation, diarrhoea, dry mouth, drowsiness	More studies are required about its efficiency
CITALOPRAM	Citalopram DG Citalvir® Seropram® Etabel® Relapaz® Somac®	Tab: 10-20-30-40 mg	**Depression:** normal dose 20 mg/day	Nervousness, drowsiness, cephalea, nausea, vomiting, constipation, dry mouth	Low sedative profile. Less risk of interactions
CLOMETIAZOL	Distraneurine®	Caps: 192 mg	**Insomnia/Anxiety:** 192 mg	Drowsiness, sedation	Can be useful to avoid delirium
CLONAZEPAM	Rivotril®	Tab: 0.5-2 mg Drops: 2.5 mg/ml Ampoules: 1 mg	**Anxiety:** 4-8 mg/day in 3 or 4 doses or 0.5-1 mg on demand **Secondary prevention of convulsive crises:** 3-6 mg/day distributed in 3 doses **Opioid-induced myoclonus:** OR, normal dose: 3-5 mg/day; IV: 1 mg in slow IV injection or slow IV perfusion	Drowsiness, sedation	Maintenance and daily anxiety Can be administered by SC route*
CLOPERASTIN	Flutox® Sekisan®	Tab: 10 mg Syrup: 17.7 mg/5 ml	**Cough:** 10-20 mg/8 h	Dry mouth, drowsiness, sedation, constipation, blurred vision	Non opioid
DIPOTASSIUM CLORAZEPATE	Tranxilium®	Caps: 5-10-15 mg Tab: 50 mg Phial: 20-50 mg Sachet: 2.5 mg	**Dyspnoea associated with anxiety:** OR: 5-10 mg on demand or series 7.5-25 mg/day in 2-3 doses	Drowsiness, sedation	
CLORPOMAZIN	Largactil®	Tab: 25-100 mg Drops. 40 mg/ml Phial: 25 mg	**Dyspnoea:** OR: 7.5-25 mg/6-8 h or on demand **Hiccups:** OR, IM: 25 mg/6- 8 h **Nausea/Vomiting:** OR, IV: 25-50 mg/6-8 h	Extrapyramidal symptoms, hypotension, fever, malignant neuroleptic syndrome, drowsiness, agitation, insomnia, nasal congestion, arrhythmias, urinary retention, dry mouth, blurred vision	The IM route can be painful
TROSPIUM CHLORIDE	Spamo Urgenin® Uraplex®	Tab: 20 mg	**Vesical Tenesmus:** 20 mg/12 h	Dry mouth, constipation, blurred vision, ocular dryness, drowsiness, urination difficulty, palpitations, tachycardia, disorientation, flatulence, chest pain, dyspnoea, rash, asthenia	

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
CODEINE	Codeisan® (tablets) Perduretas codeína® (retard tablets) Bisoltus® Histaverin® Codeisan jarabe® Codulin® Notusin® Fludan Codeína® (syrups)	Tab: 28.7 mg Tab Retard: 50 mg Syrup-solution: 6.33-10 mg/5 ml	**Pain:** 30-60 mg/4-6 h **Cough:** 10-120 mg/4-6 h **Diarrhoea:** 30 mg/6 h	Constipation, paralytic ileus, drowsiness, respiratory depression, nausea	May be necessary to associate laxative (in pain, cough)
CHOLESTYRAMINE	Lismol® Resincolestiramina®	Sachets: 5 g	**Cholestasis-induced pruritus:** 4 g/8 h	Constipation, diarrhoea, nausea, vomiting, abdominal problems	
DISODIUM CROMOGLYCATE	Alergocrom® Frenal® Nebulasma® Nebulcrom®	Powder for inhaling: 20 mg/capsule	**Cough:** 20 mg/6 h inhaled	Transitory bronchospasm, cough, pharyngeal irritation	In case of failure of previous treatments in lung cancer
DANAZOL	Danatrol®	Caps: 50-100-200 mg	**Cholestasis-induced pruritus:** 100 mg/1-3 times a day	Nausea, dizziness, skin reactions, photosensitivity, fever, nervousness, back pain, muscular spasm, anxiety, vertigo, acne, hirsutism, leucopoenia, thrombopoenia	
DEXAMETASONE	Dexametasone Fortecortin® Dalamon® Injectable	Tab: 1 mg Ampoules: 4 mg	**Anorexia/cachexia:** OR, SC: 3-8 mg/day **Dysphagia:** (if inflammation) OR, SC, IV: 4-8 mg/day **Nausea and vomiting unrelated to chemotherapy:** OR, SC, IV: 4-16 mg/day Normal dose used in studies for prevention in chemotherapy: IV: 20 mg/day **Intestinal obstruction:** IV, SC: 4-16 mg/day **Spinal cord compression:** IV bolus initial 10-100 mg, followed by dose of 16 mg/OR (dose use in clinical trials)	Hyperglycaemia, myopathy, Cushing syndrome, osteonecrosis, psychic disorders (hypomania, depression, insomnia, apathy, psychosis) dyspepsia, ulcus, hydrosaline retention, HBP	Can be administered by SC route*, but not mixed with other drugs in SC infusion In short series (up to 3 weeks) gradual withdrawal is not usually required.

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
DEXCLORFENI-RAMINE	Plaramine®	Tab: 2 mg Repetabs: 6 mg Syrup: 2 mg/5 ml Ampoules: 5 mg	**Uraemia-induced and dry skin pruritus**: OR: 2 mg/6-8 h, IV: 5 mg/6-8	Drowsiness, dry mouth, blurred vision, nausea, cephalea	
DEXTROMETOR-PHANE	Aquitos® Bexatus® Bisolvon Antitusivo® Cinfatos® Formulatus® Frenatus® Ilvitus® Parilatos® Romilar® Serratos® Streptuss® Tusorama® Tussidrill®	Tab: 10-15-20 mg Solution: 10 mg/5 ml Syrup: 10-15 mg/5 ml	**Cough:** 10-20 mg/4-6 h or 30 mg/8 h	Nausea, vomiting, abdominal pain, drowsiness	Precaution in hepatic failure. Some presentations are not fundable
DIAZEPAM	Diazepam GD Valium® Stesolid®	Tab: 5-10 mg Ampoules: 10 mg Suppositories: 5-10 mg Micro-enema: 5-10 mg	**Insomnia:** 5-10 mg at bedtime **Convulsive crises:** 5-10 mg rectal route-IV IV infusion: 2.5-5 mg/minute	Drowsiness, sedation	
DICLOFENAC	Diclofenac GD Voltaren® Dolotren® Dolo Nervobion® Luase®	Tab: 50 mg Tab Retard: 75-100 mg Suppositories: 100 mg Ampoules: 75 mg Maximum dose: 150 mg/day	**Pain:** Oral: 50 mg/8 h Oral retard: 75-150 mg/24 h Rectal: 100 mg/24 h IM-IV: 75 mg/24 h (exceptionally 150 mg/24 h)	Gastropathy, ulcus, renal functional deterioration, oedemas, confusion, asthma precipitation, angio-oedema, rash	Adjust dose in older people and renal failure It use is admitted in patients taking oral anti-coagulants. It can be used in continuous infusion by SC route (not in bolus), but do not mix with other drugs*
DIHYDROCODEINE	Paracodina® Tosidrin®	Syrup: 12 mg/5 ml	**Cough:** 6-10 mg/4-6 h **Pain:** 30 mg/4-6 h	Constipation, nausea, vomiting	Not marketed in Spain in tables or phials. May be necessary to associate laxative
DIMENHYDRATE	Biodramina® Cinfamar® Travel well ®	Tab: 25-50 mg Oral solution: 20 mg/5 ml Suppositories: 100 mg Drinkable ampoules: 15.75 mg	**Nausea and vomiting** of vestibular origin: OR, rectal: 60-100 mg/4-6 h	Drowsiness, anticholinergic effects	Not fundable

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
DOMPERIDONE	Domperidona® Motilium®	Tab, Caps: 10 mg Susp: 5 mg/5 ml Suppos: 30-60 m	**Nausea and vomiting of vestibular origin:** OR: 10-20 mg/6-8 h Rectal route: 60 mg/8 h	Extrapyramidal effects are rare	
DULOXETIN	Cymbalta® Xeristar®	Gastro-resistant cap: 30-60 mg	**Neuropathic pain:** Initial dose: 60 mg/day in single dose Normal dose: 60 mg/day DM: 120 mg/day in divided dose	Nausea, dry mouth, cephalea, constipation	Approved in technical data sheet for diabetic neuropathy Treatment must be withdrawn gradually
SPIRONOLACTONE	Spironolactone DG Aldactone A® Aldactone 100®	Tab: 25-100 mg	**Ascites:** 100/400 mg/day	Impotence, gynecomastia, lethargy, cephalea, confusion, hyperpotasemia, hyponatremia	
FENITOINE	Epanutin® Neosidantoina® Singergina®	Caps: 100 mg	**Secondary prevention of convulsive crises:** 4-8 mg/kg/day divided into 3 doses	Nausea, vomiting, mental confusion, dizziness, cephalea, shaking, insomnia, dyskinesias, ataxia, nystagmus, blurred vision, skin rash, gingival hypertrophy	Narrow therapeutic margin May induce numerous interactions
FENOBARBITAL	Luminal® Cardenal® Gratusminal®	Tab: 50-100 mg Drops: 126 mg/ml Ampoules: 200 mg	**Secondary prevention of convulsive crises:** OR: 60-250 mg/day divided into 2 doses **SC route sedation:** Induction: 100-200 mg SC perfusion: 600 mg/day, Rescue: 100 mg bolus **IV route sedation.** Induction: 2 mg(kg slow, Perfusion: 1 mg/kg/h and modify according to response	Dizziness, lethargy, ataxia, confusion, skin reactions, excitation, uneasiness, megaloblastic anaemia	Can be administered by SC route
FENTANYL	Prolonged release patch: Fentanyl GD Durogesic Matrix® Rapid release: Actiq® (oral dissolution tab)	Patches: 12-25-50-75-100 µg Oral dissolution tab: 0.2-0.4-0.6-0.8-1.2-1.6 mg	**Pain:** Initial dose in patients not treated with opioids: 25 mcg/72 h in patch, increasing dose by 25 mcg/h until efficient dose. Treated with morphine: according to morphine dose. Irruptive pain or rescue: 0.2-1.6 mg on demand the dose cannot be predicted based on maintenance dose)	Nausea, vomiting, constipation, drowsiness, dry mouth, perspiration, respiratory depression, hallucinations, dysphoria, urinary retention, myoclonus, local rash due to patch	The increase in temperature increases its absorption Change of patch every 48 h is required on occasions Associate laxative Useful in rotation of opioids
FLUCONAZOL	Fluconazol GD Diflucan® Lotin®	Caps: 50-100-150-200 mg Suspension: 50-200 mg/5 ml Phial: 200-400 mg	**Prevention of oral candidiasis:** 50 mg/12 h	Nausea, vomiting, abdominal pain, cephalea, pruritus, photophobia, dizziness, hepatopathy	Precaution in hepatopathy

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
FLUOXETINE	Fluoxetine GD Adofen® Prozac® Reneuron® Lecimar® Luramon® Nodepe®	Caps: 20 mg Solution: 20 mg/5 ml	**Depression:** 20-40 mg/day Normal dose: 20 mg	Nausea, vomiting, diarrhoea, dyspepsia, anorexia, skin rash, arthromyalgias, dry mouth, shakiness, hallucinations, drowsiness, vasodilatation, pharyngitis, dyspnoea	Start with low doses in older people (10 mg) Precaution in diabetes, renal failure and epileptics
PHOSPHATES	Enema Casen®	Rectal suspension	**Constipation/Faecal Impaction:** 1-2 enemas according to response	Local irritation	Not fundable
FUROSEMIDE	Furosemide GD Seguril®	Tab: 40 mg Ampoules: 20-250 mg	**Ascites:** OR, -IM-IV-SC: 40-80 mg/day	Hyponatremia, hypopotasemia, hypotension, nausea, gout, hyperglycaemia	Risk of dehydration and hypopotasemia Can be administered by SC route*
GABAPENTIN	Gabapentin GD Gabatur® Neurontin®	Tab or caps: 300-400-600-800 mg	**Neuropathic pain:** Initial dose: 300 mg 1st day, 300 mg/12 h 2nd day, 300 mg/8 h 3rd day Increase dose by 300 mg/day Normal dose: 1200-1400 mg/day (2 or 3 doses) **Hiccups:** 300-600 mg/8 h **Secondary prevention of convulsive crises:** 100-400 mg/8 h Maximum dose: 3600 mg/day	Drowsiness, lack of stability, nausea, oedema, diplopia	Reduce dose in renal failure and in the older people
GLYCERINE	Glycerine suppositories	Suppositories: 0.92-1.85-2.7 g	**Constipation:** 1 suppository/24 h	Proctitis, anal stinging	Not fundable
HALOPERIDOL	Haloperidol®	Tab: 0.5-10 mg Drops: 2 mg/ml Ampoules: 5 mg	**Delirium:** Range of normal dose OR, SC, IM, IV: 0.5-5 mg/2-12 h Normal dose OR: 1-3 mg/8 h Normal dose SC bolus: 2.5 mg(every 30 minutes, maximum 3 times) Normal dose SC infusion: 5-15 mg/day **Nausea and vomiting:** OR, SC, IV: 1.5-5 MG(DAY **Hiccups:** OR 3 mg at night **Anxiety:** OR: 1.5.5 mg on demand or series 3-10 g/l h	Extrapyramidal symptoms (dystonia and akathisia) hypotension, fever, malignant neuroleptic syndrome, drowsiness, agitation, insomnia, nasal congestion, arrhythmias, urinary retention, dry mouth, blurred vision	Can be administered by SC route*
HYDROXICINE	Atarax®	Tab: 25 mg Syrup: 10 mg/5 ml	**Uraemia-induced and dry skin pruritus**: 25 mg/8-24 h.	Drowsiness, dry mouth, blurred vision, nausea, cephalea	

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
IBANDRONIC ACID	Bondronat®	Tab: 50 mg Phial: 2-6 mg	**Hypercalcaemia:** Solution for IV perfusion: 2-4 mg in 15 minutes at least (diluted with 100 ml sodium chloride at 0.9% or glucosate 5%)	Fever, pseudoinfluenza, nausea, anorexia, abdominal pain, diarrhoea, constipation, arthralgia, myalgias, anaemia	Maintain good hydration Hospital use
IBUPROFEN	Ibuprofen GD Algiasin® Espidifen® Neobrufen® Dolorac® Saetil®	Tab: 400-600 mg Sachets: 400-600 mg Suppositories: 500 mg (Gelofen)	**Pain and fever:** OR: 400-600 mg/6-8 h Rectal: 600 mg/8 h Maximum dose: 2400 mg/day **Vesical tenesmus:** OR: 400-600 mg/8 h Rectal: 500 mg/8 h	Gastropathy, ulcus, renal functional deterioration, oedemas, confusion, asthma precipitation, angio-oedema, rash	Adjust dose in older people and renal failure Patients who take oral anti-coagulants
IMIPRAMIN	Tofranil®	Tab: 10-25-50 mg Caps: 75-150 mg	**Vesical tenesmus:** 25-50 mg/day **Antidepressant:** 50-100 mg/day	Dry mouth, sedation, urinary retention, orthostatic hypotension, cardiovascular disturbances	Precaution in patients with arrhythmia or ischemic cardiopathy
ISPAGHULA (ovate plantain)	Plantago ovata® Metamuci® Pantaben®	Sachets: 3.5 g	**Constipation:** OR: 3.5-10 g/day	Flatulence, abdominal distension	Maintain good hydration to avoid obstruction Bulk-forming laxative Fundable
ITRACONAZOL	Itraconazol GD Canadiol® Hongoseril® Sporanox®	Caps: 100 mg Suspension: 50 mg/5 ml Phial: 250 mg	**Prevention of oral candidiasis:** 100 mg/12 h	Nausea, vomiting, abdominal pain, cephalea, pruritus, photophobia, dizziness, hepatopathy	Precaution in hepatopathy
KETOCONAZOL	Fungarest® Fungo zeus® Ketoisdin® Micoticum® Panfungol®	Tab: 200 mg Suspension: 100 mg/5 ml	**Prevention of oral candidiasis:** 400 mg/12 h	Nausea, vomiting, abdominal pain, cephalea, pruritus, photophobia, dizziness, hepatopathy	Precaution in hepatopathy
KETOROLAC	Algikey® Droal® Tonum® Toradol®	Tab: 10 mg Ampoules: 10-30 mg	**Pain:** OR: 10 mg/6-8 h IV_IM-SC: 10-30 mg/6-8 h Maximum dose: 40 mg/day	Gastropathy, ulcus, renal functional deterioration, oedemas, confusion, asthma precipitation, angio-oedema, rash	Adjust dose in older people and renal failure Possible interaction with oral anticoagulants The NSAIDs are the first option in bone pain Greater haemorrhage risk than other NSAIDs Drug of “hospital use” Can be used by SC route, but do not mix with other drugs”

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
LACTULOSE	Lactulose Duphalac® Belmalax®	Solution: 3.33 g/5 ml Sachets: 10 g	**Constipation:** Treatment of chronic constipation: initially 15 ml(10 mg)/12 h, after 2-3 days 15-30 ml/day Prevention of constipation: 15 ml (10 mg)/8-24 h.	Flatulence, colic, abdominal problems, cramps	May take up to 3 days in have effect Osmotic laxative
LAMOTRIGINE	Lamotrigine GD Lamictal® Labileno® Crisomet®	Dispersible tab: 2-5-25-50-100-200 mg	**Secondary prevention of convulsive crises:** 100-200 mg/day divided into 2 doses	Skin rash, nausea, vomiting, diarrhoea, fever, lymphadenopathies, hepatic dysfunction, blood disturbances, confusion hallucinations, nystagmus, diplopia, blurred vision	
LEVODROPRO-PIZIN	Levotuss® Tautoss®	Drops: 60 mg/ml Syrup: 30 mg/5 ml	**Cough:** 60 mg/8 h	Skin rash, nausea, pyrosis, dyspepsia, diarrhoea, asthenia, drowsiness, cephalea, vertigo	Non-opioid
LEVOMEPRO-MAZIN	Sinogan®	Tab: 25-100 mg Drops: 40 mg/ml Ampoules: 25 mg	**Dyspnoea:** OR, SC: 2.5-10 mg **Delirium:** Range of normal dose OR, SC, IM: 12.5-50 mg/4-12 h Normal dose SC bolus: 12.5 mg(every 30 minutes, maximum 3 times) Normal dose in SC infusion: 50-200 mg/day **Anxiety:** OR: 25-75 mg/day in 2-3 doses **SC route sedation:** Induction: 12.5-25 mg, Perfusion: 100 mg/day, Rescue: 12.5 mg **IV route sedation:** half the dose used by SC route	Drowsiness, sedation, dry mouth constipation, urinary retention, extrapyramidal symptoms	Can be used by SC route* (levomepromazin is also known as methotrimeprazin). More sedative than haloperidol, alternative to haloperidol in patient with delirium with intense agitation.
LIDOCAINE	Lidocaine Xilonibsa® Octocaine®	Ampoules at 2%	**Cough:** 5 ml/6-8 h sprayed	Aspiration risk	
LOPERAMIDE	Loperamide Fortase® Elissan® Imodium® Loperan® Protector® Salvacolina® Taguino® Loperkey® Imodium Flas®	Tab: 2 mg Suspension: 0.2 mg/ml Liotabs: 2 mg(Imodium Flas)	**Diarrhoea:** Initial dose 4 mg and followed by 2 mg after each bowel movement until a maximum of 16 mg/day	Abdominal pain, dizziness, drowsiness, hive, paralytic ileum, abdominal distension	

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
LORATADINE	Loratadine GD Civeran® Clarytine® Velodan®	Tab: 10 mg Syrup: 5 mg/5 ml	**Uraemia-induced and dry skin pruritus:** OR: 10 mg/day	Less sedative than traditional anti-histamines	
LORAZEPAM	Lorazepam GD Idalprem® Orfidal®	Tab: 1-5 mg	**Dyspnoea with anxiety: OR: 0.5-1 mg/4-12 h** or on demand **Insomnia:** OR: 0.5-2 mg at bedtime **Anticipatory vomiting:** OR: 2-4 mg/day	Somnolence, confusion, ataxia, amnesia, dependence, muscular weakness, hypotension, dysarthry, urinary incontinence	Intermediate duration. Induction and maintenance of sleep Low daytime sedation
LORMETAZEPAM	Lormetazepam GD Noctamid® Loramet®	Tab: 1-2 mg	**Insomnia:** OR: 0.5-2 mg at bedtime	Somnolence, confusion, ataxia, amnesia, dependence, muscular weakness, hypotension, dysarthry, urinary incontinence	Intermediate duration. Induction and maintenance of sleep Low daytime sedation
MAGNESIUM SALTS	Eupeptina® Magnesia Cinfa® Magnesia San Pellegrino®	Suspension: 1 g/5 ml Sachets: 2.4-3.6 g	**Constipation:** OR: 2.4-3.6 g/day	Risk of hypermagnesaemia in renal failure	Not fundable
ACETATE MEGESTROL	Borea® Maygace® Megefren®	Tab: 40-160 mg Sachets: 160 mg Suspension: 200 mg/5 ml (Maygace High Doses)	**Anorexia/cachexia:** OR initial dose: 160 mg/day OR normal dose: 320-800 mg/day Maximum dose: 800 mg/day	Nausea, vomiting, weakness, oedema, breast strain, alopecia, flush	Its effect takes weeks to appear so it is recommended in patients with life expectation >2-3 months
METHADONE	Metasedin®	Tab: 5-30-40 mg Ampoules: 10 mg	**Pain:** OR, SC, IM: initial dose: 5-10 mg/6-8 h adapted according to response If used in a prolonged manner do not administered with intervals of less than 12 h.	Nausea, vomiting, constipation, drowsiness, dry mouth, perspiration, respiratory depression, hallucinations, dysphoria, urinary retention, myoclonus	Long average life with risk of accumulation Renal and hepatic failure do not interfere in its elimination Great inter-individual variability in dose Handling by expert personnel Useful in opioid rotation Associate laxative Can be administered by SC route
METAMIZOL (dypirone)	Metamizol GD Nolotil® Lasain® Algi Mabo® Dolemicin®	Capsules: 500/575 mg Sachets: 500-1000 mg Suppositories: 1000 mg Ampoules: 2000 mg	**Pain and fever:** OR: 500-2000 mg/6- 8 h Rectal: 1000 mg/6-8 h IV-IM: 2000 mg/6-8 h	Skin reaction, agranulocytosis, aplastic anaemia, hypotension, anaphylaxia	

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
METHYLFENIDATE	Rubifen® Omozin®	Tab: 5-10-20 mg Prolonged rel. tab: 18-38-54 mg	**Anorexia/cachexia:** OR: 5-15 mg/day **Depression:** OR: 5-30 mg/day	Abdominal pain, nausea, dry mouth, tachycardia, arrhythmias, insomnia, nervousness, dizziness, angina, psychosis	More studies are required on its efficiency. Contraindications: angina, arrhythmias or serious HBP, serious depression, psychotic symptoms, suicide tendencies Administer in the morning or midday due to possible insomnia effect
METHYLCELLUOSE	Muziplasma®	Caps: 500 mg.	**Constipation:** OR: 1500 mg/24 h	Flatulence, abdominal distension	Maintain good hydration to avoid obstruction. Bulk forming laxative Not fundable
METHYLPREDNI-SOLONE	Methylpredni-solone Urbason® Solu Moderin®	Tab: 4-16-40 mg Phial: 8-20-40-125-250-500-1000 mg	**Anorexia/cachexia:** OR: 32 mg/day IV: 125 mg/day (dose used in clinical trials)	Hyperglycaemia, myopathy, Cushing syndrome, osteonecrosis, psychic disorders (hypomania, depression, insomnia, apathy, psychosis), dyspepsia, ulcus, hydrosaline retention, HBP	In short series (up to 3 weeks) gradual withdrawal is not usually required
METOCLOPRA-MIDE	Primperan®	Tab: 10 mg Drops: 2.6 mg/ml Solution: 5 mg/5 ml Ampoules: 100 mg	**Nausea and vomiting:** Normal dose OR, SC, IM, IV: 15-60 mg/day in 2-4 doses SC infusion: 30-100 mg/day Nausea and vomiting related to chemotherapy (parenteral route): 40-60 mg/day **Hiccups:** OR, IV, SC: 10 mg/6-8 h	Extrapyramidal effects, drowsiness, agitation, diarrhoea, depression, arrhythmias by IV route	Contraindicated in bowel obstruction Can be administered by SC route*
METRONIDAZOLE	Metronidazol Viñas ® Rozex®	Gel 0.75%	**Neoplastic skin ulcer:** 1 application/8 h	Skin irritation	Avoid exposure to sun
MIANSERIN	Lantanon®	Tab: 1030 mg	**Depression:** 20-60 mg/day	Minimum anticholinergic effects. Precaution in patients with diabetes mellitus, epilepsy and hepatic or renal failure	In one or several daily doses
MIDAZOLAM	Midazolam GD Dormicum®	Tab: 7.5 mg Ampoules: 5-15-50 mg	**Convulsive crisis:** IV, SC: 10-15 mg **Opioid-induced myoclonus:** OR, IV, SC: 5-10 mg **Untreatable hiccups:** 5-10 mg bolus IV-SC and continue with perfusion of 30-60 mg/day	Increase in appetite, jaundice, hypotension, disturbance of cardiac rhythm, anaphylaxis, thrombosis, bronchospasm, respiratory depression, drowsiness, confusion, ataxia, amnesia, hallucinations, muscular weakness	Can be administered by SC route* Ampoules of Hospital use

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
MIDAZOLAM			**Dyspnoea with anxiety:** OR: 7.5 mg on demand or series 7.5 mg/8 h **Delirium with intense agitation:** SC bolus, IV. 2.5-5 mg and repeat until it stops. Maintenance in IV perfusion, SC: 20-100 mg/day **SC route sedation:** Induction: 2.5-5 mg Perfusion: 0.4-0.8 mg/h Rescue: 2.5-5 mg bolus Double dose is benzodiazepines taken previously **IV route sedation:** Induction: 1.5-3 mg every 5 min until sedated (the dose required will be the induction dose) Perfusion: induction dose x 6 Rescue: induction dose Maximum dose: 200 mg/day		
MILTEFOSINE	Miltex®	6% solution 6% cream	**Neoplastic skin ulcer:** 1-2 applications/day	Local intolerance, skin irritation, nausea, vomiting	Medication of hospital diagnosis
MIRTAZAPINE	Mirtazapine GD Vastat® Rexer®	Tab: 15-30 mg Solution: 15 mg/ml	**Insomnia associated with depression and/or anorexia:** 15-30 mg at bedtime **Uraemia-induced or paraneoplastic pruritus:** 7.5-15 mg/day	Increase in appetite, oedema, sedation, postural hypotension, anomalous fantasies, mania, trembling, convulsion, arthralgias, akathisia.	The presentation of oral dispersible tablets exists
MODAFINIL	Modiodal®	Tab: 100 mg	**Anorexia/cachexia:** OR: 200-400 mg/day	Abdominal pain, nausea, dry mouth, tachycardia, arrhythmias, insomnia, nervousness, dizziness, angina, psychosis	More studies on its efficiency are required, little experience of use Contraindicated in serious anxiety Precaution in renal, hepatic failure, cardiovascular disturbances, depression, mania and psychosis

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
MORPHINE	Prolonged release: MST Continus® MST Unicontinus® Skenan® Rapid release: Sevredol® Oral solution rapid release: Oramorph® Injection: Cloruro mórfico®	Tab: 10-15-30-60-100-200 mg Caps: 30-90-120 mg Sachets: 30 mg Ampoules: 10-20 mg	**Pain:** OR: 10-30 mg/4 h Retard forms: 10-30 mg/12 h SC-IM route: half of OR dose Increases in dose: 25-50% of the dose The dose can be doubled at bedtime to avoid one dose **Irruptive pain:** 1/6 of the total daily dose (rapid release) **Dyspnoea:** If not receiving morphine treatment: OR, SC: 2.5-5 mg/4 h. If receiving morphine treatment: increase dose by 25-50% **Cough: OR: 2.5-5 mg/4-6 h**	Nausea, vomiting, constipation, drowsiness, dry mouth, perspiration, respiratory depression, hallucinations, dysphoria, urinary retention, myoclonus	It has no therapeutic ceiling except for the appearance of adverse effects Associate laxative Antidote: Naloxone Can be administered by SC route
NALTREXONE	Antaxone® Celupan® Revia®	Caps: 25 mg Coated tab: 50 mg	**Cholestasis-induced pruritus:** OR: Onset 12.5/12 h. Increase to maintenance dose 50-300 mg/day	Nausea, vomiting, abdominal pain, anxiety, nervousness, insomnia, diarrhoea, constipation, dizziness, irritability	Antagonises the effects of opioids
NAPROXEN	Naproxen GD Aliviomas® Antalgin® Denaxpren® Lundiran® Momen® Naproxyn® Nacron®	Caps: 230 mg Coat. Tab: 550-500 mg Enteric tab: 250-500 mg Sachets: 200-500 mg Suppositories: 500 mg	**Pain:** OR or rectal: 500 mg/12 h **Vesical tenesmus:** OR, rectal: 500 mg/12 h	Gastropathy, ulcus, renal function deterioration, oedemas, confusion, asthma precipitation, angio-oedema, rash	Adjust dose in older people and renal failure Possible interaction with oral anticoagulants NSAIDs are the first option in bone pain
NIFEDIPINE	Nifedipine GD Adalat®	Caps: 10 mg	**Hiccups**: OR: 10-20 mg/8 h	Cephalea, flushing, dizziness, palpitations, tachycardia, hypotension, oedema, pruritus, hives, constipation or diarrhoea, asthenia, paresthesia.	May produce hypotension, above all by SL route
OCTREOTIDE	Sandostatin®	Phial: 50-100µg	**Diarrhoea (refractory):** SC: 50-500 µg/day **Bowel obstruction:** SC: 300-800 µg/day, SC Infusion: 300-600 µg/day Maximum dose: 1500 µg/day	Nausea, vomiting	Can be administered by SC route Medication of hospital diagnosis (indications not included in technical data sheet)

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
OMEPRAZOL	Omeprazol GD Audazol® Belmazol® Gastrimu® Omapren® Parizac® Ulceral® Ulcometion®	Caps: 20-40 mg Phial: 40 mg	**Hiccups:** 20 mg/day	Nausea, vomiting, abdominal pain, flatulence, diarrhoea, cephalea, dizziness, dry mouth, drowsiness, insomnia, blurred vision, hypersensitivity react, confusion, agitation, hallucinations	
ONDANSETRON*	Ondansetrón EFG Yatrox® Zofran®	Tab: 4-8 mg Ampoules: 4-8 mg	**Nausea and vomiting:** OR, SC, IV: 12-24 mg/day Variable via of administration and dose according to emetic risk **Uremic pruritus and opioid induced pruritus:** OR, SC: 4-8 mg/8 h	Constipation, headache, sensation of warmth or flushing, hiccups, visual disorders, dizziness, involuntary movements, convulsions	It increases its efficacy when associated to dexamethasone. It can be administered subcutaneously Tablets: hospital diagnosis Ampoules: hospital use
OXYBUTYNIN	Ditropan® Drsplan®	Tab: 5 mg	**Vesical tenesmus:** 2.5-5 mg/6-12 h	Dry mouth, constipation, blurred vision, dry eyes, drowsiness, urination difficulty, palpitations, tachycardia, disorientation, anorexia, face flushing	
OXYCODONE	Prolonged release: Oxycontin® Rapid release: Oxynorm®	Prolonged release tab: 10-20-40-80 mg Rapid release caps: 4.5-9-18 mg Oral solution: 10 mg/ml	**Pain:** Initial dose: 10 mg/12 h Rapid release (irruptive pain): 4.5-18 mg on demand	Nausea, vomiting, constipation, drowsiness, dry mouth, perspiration, respiratory depression, hallucinations, dysphoria, urinary retention, myoclonus	Adjust dose in renal and hepatic failure Associate laxative
PALIFERMIN	Kepivance® 6.25 mg powder	Phials: 6.25 mg	**Mucositis** in patients with haematological neoplasias submitted to myeloablative treatment: IV: 60 mc/kg/day, 3 days before and 3 after myeloablative treatment	Taste alteration, thickening or fading of skin, rash, pruritus and erythema, arthralgia, oedema, pain and fever	Medication for Hospital use
PAMIDRONIC ACID	Aredia® Linoten® Pamifos® Xinsodona®	Phial: 15-30-60-90 mg	**Bone pain:** IV perfusion: 90 mg in 250 ml in 2 h every 3-4 weeks In patients with multiple myeloma do not exceed 90 mg in 500 ml for 4 h **Hypercalcaemia:** IV Perfusion: 30-90 mg in 2-4 h (do not exceed 90 mg in 500 ml for 4 hours)	Fever, pseudoinfluenza, nausea, anorexia, abdominal pain, diarrhoea, constipation, arthralgias, myalgias, anaemia	Precaution in cardiopaths and renal failure Maxillary osteonecrosis has been described (dental revision prior to treatment is recommend) Hospital use

*** INFORMATION NOTE Spanish Agency of Medicines and Medical Devices (10th August 2012):**
Due the potential risk of arrhytmias, there are new recommendations for the use of ondansetron. The maximum single intravenous dose of ondansetron for chemotherapy induced nausea and vomiting is 16 mg. More information available at:
http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_FV_14-2012.htm (NOTE: website in spanish)

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
PARACETAMOL	Paracetamol GD Termalgin® Efferalgan® Zumadol® Gelocatil® Dolostop®	Tab: 500/650/1000 mg Efferv. Tab: 1000 mg Sachets: 650/1000 mg Suppositories; 650 mg IV Phial: 1000 mg	**Pain and fever:** OR: 500-1000 mg/4-6 h Rectal: 650 mg/4-6 h IV: 1000 mg/6 h Maximum dose: 4 g/day	Scarce toxicity. Rash, hepatic toxicity, fever	
PARACEMATOL+ CODEINE	Anagiplus® Apiretal codeína® Cod efferalgan® Coxumadol® Dolgesic codeína® Dolomedil® Fludeten® Gelocatil codeína ® Termalgin codeína®	Tab: 500/30, 500/15 mg, 500/10, 325/15, 650/30, 300/30 Efferv. Tabl: 600/30 Sachets: 500/30 Caps: 300/14 Solution: 120/12 mg/5 ml Suppos: 650/28	**Pain:** OR: 500-650/30 mg 1-2 tab/6 h Maximum dose: 4 g paracetamol	See paracetamol and codeine	Association of laxative may be necessary A presentation in syrup exists but with low doses
PARAFFIN	Emuliquen simple® Hodernal®	Sachets: 7, 17 g Solution: 4 g/5 ml Emulsion: 2.39 g/5 ml	**Constipation:** OR: 15 ml/12-24 h		Not fundable
PAROXETINE	Paroxetine GD Casbol® Motivan® Frosinor® Paratonina® Seroxat®	Tab: 20 mg	**Depression:** normal dose 20 mg/day **Opioid-induced or haematological neoplastic pruritus:** 20 mg/day Start with low doses in older people (10 mg)	Nausea, vomiting, diarrhoea, dyspepsia, anorexia, skin rash, arthromyalgias, dry mouth, trembling, hallucinations, drowsiness, vasodilatation, pharyngitis, dyspnoea, yawning	Start with low doses in older people (10 mg) It takes weeks to have effect
SODIUM PICOSULPHATE	Contumax® Evacuol® Ezor® Gutalax® Lubrilax® Skilax ®	Drops: 7.5 mg/ml	**Constipation:** 5-10 mg at night	Abdominal cramps, diarrhoea	Do not administer if bowel obstruction Stimulating laxative Not fundable
PILOCARPIN	Salagen®	Tab: 5 m	**Xerostomia:** 5-10 mg8 h	Cephalea, pseudoinfluenza syndrome, perspiration, nausea, abdominal pain, constipation, flushing, HBP, palpitations, bronchial hypersecretion	Precaution: asthma and COPD, cardiovascular disease, cognitive or psychiatric disturbances. Eye drops can be used by oral route (4-6 drops(8 h. dissolved in juice

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
POLYETHYLEN-GLYCOL	Movicol®	Sachets: 13, 125 g	**Constipation:** 1 sachet/8-24 h	Abdominal distension and pain, nausea	Not fundable
POVIDONE IODINE	Betadine Oral®	External solution: 10 mg	**Mucositis:** Mouthwashes 10 ml/8-12 h	Local irritation	Not fundable
PREDNISOLONE	Estilsona®	Drops: 13.3 mg/ml	**Anorexia/cachexia:** OR. 10 mg/day (dose used in clinical trials) Dose range: 10-30 mg/day **Hypercalcaemia:** OR. 40-100 mg/day	Hyperglycaemia, myopathy, Cushing syndrome, osteonecrosis, psychic disorders (hypomania, depression, insomnia, apathy, psychosis), dyspepsia, ulcus, hydrosaline retention, HBP	In short series (up to 3 weeks) gradual withdrawal is not normally required
PREDNISONE	Prednison Dacortin®	Tab: 2.5-5-10-30-50 m	**Asthenia:** 20-40 mg/day **Dyspnoea** in patients with asthma, COPD, carcinomatous lymphangitis or obstructive tumours of airway: OR: 20-40 mg/day	Hyperglycaemia, myopathy, Cushing sd. Osteonecrosis, psychic disorders (hypomania, depression, insomnia, apathy, psychosis), dyspepsia, ulcus, hydrosaline retention, HBP	Its effect is temporary (2-4 weeks) so it is recommended in patients with <4 week life expectation In short series (up to 3 weeks) gradual withdrawal is not normally required
PREGABALIN	Lyrica®	Caps: 25-75-150-300 mg	**Neuropathic pain:** Initial dose: 50-150 mg/day in 2-3 doses. Increase by 50-150 mg every week Normal dose: 300-600 mg/day Maximum dose: 600 mg/day	Dizziness, drowsiness, ataxia, reduced concentration, trembling, tachycardia, gastrointestinal effects, blurred vision, diplopia, vertigo, erectile dysfunction, asthenia, polydipsia	Reduce dose in renal failure and older people
PROMETAZIN	Frinova®	Syrup: 6 mg/6 ml	**Dyspnoea:** OR, IM, IV: 25 mg/8-12 h or on demand	Orthostatic hypotension, extrapyramidal symptoms	As an adjuvant or second line drug, if opioids cannot be administered or associated with these
PROPOFOL	Propofol Ivofol® Recofol® Diprivan®	Phials: 10-20 mg	**IV Sedation:** Induction: 1-1.5 mg/kg Perfusion: 2 mg/kg/h, Rescue: bolus of 50% the induction dose	Nausea, hypotension, cough, bradycardia, cephaleas, dizziness, trembling, vomiting, phlebitis	Previously suspend perfusion or BZD or neuroleptics and reduce opioids to half For hospital use
RIFAMPICINE	Rifaldin® Rimactan®	Caps: 300-600 mg Suspension: 100 mg/5 ml Phial: 600 mg	**Cholestasis-induced pruritus:** OR: 300-600 mg/8-12 h	Anorexia, nausea, vomiting, diarrhoeas, cephalea, drowsiness, pseudoinfluenza, haemolytic anaemia, oedema, muscular weakness, disturbance of hepatic tests	Colours urine, saliva and other body fluids orange

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
SALBUTAMOL	Salbutamol GD Ventolin® Buto air ® Buto asma® Ventilasen®	Aerosol: 100 mcg/squirt Cartridge: 100 mcg/dose Breathing solution: 0.5%	**Dyspnoea** in patients with reversible obstruction: inhaled 1-2 squirts on demand	Palpitations, cephalea, trembling	
SEN (Cassia angustifolia)	Laxante Descansa Normal® Laxante Salud® Laxante Olan®	Tab: 7.5 mg	**Constipation:** 7.5 mg/8-24 h	Do not administer if bowel obstruction	Stimulating laxative Not fundable
SENOSIDES A and B	Modane® Puntual® Pursenid®	Tab: 12 mg Drop solution: 30 mg/ml	**Constipation:** 12-36 mg/24 h	Do not administer if bowel obstruction	Stimulating laxative Not fundable
SERTRALINE	Sertraline GD Vestirán® Aremis® Altisben® Depesert®	Tab: 50-100 mg	**Depression:** 50-200 mg	Nausea, vomiting, diarrhoea, dyspepsia, anorexia, skin rash, arthromyalgias, dry mouth, trembling, hallucinations, drowsiness, vasodilatation, pharyngitis, dyspnoea	More sedative than fluoxetine, less risk of interactions. Contraindicated in epileptic patients or with renal or hepatic failure
TIETILPERAZINE	Torecan®	Tabs: 6.5 mg Suppositories: 6.5 mg	**Nausea and vomiting** of vestibular origin: OR, rectal: 6.5 mg/8-24 h	Sedation, drowsiness, digestive disturbances	Antihistamine
TOLTERODIN	Detrusitol® Urotrol®	Tab: 2 mg	**Vesical tenesmus:** 2 mg/12 h	Dry mouth, constipation, blurred vision, dry eyes, drowsiness, urination difficulty, palpitations, tachycardia, disorientation, dyspepsia, fatigue, flatulence, chest pain, oedema, paresthesia	
TOPIRAMATE	Topamax® Bipomax®	Caps: 15-25-50 mg Tab: 25-50-100-200 mg	**Secondary prevention of convulsive crises:** 100-200 mg/12 h	Nausea, abdominal pain, dyspepsia, dry mouth, disgeusia, weight loss, paresthesia, cephalea, fatigue, dizziness, language disturbance, drowsiness, insomnia, memory and concentration disturbance, anxiety, depression	

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
TRAMADOL	Tramadol GD Adolonta® Dolodol® Ceparidin® Tioner® Tralgiol®	Caps: 50 mg Drops: 100 mg/ml Suppositories: 100 mg Phial: 100 mg	**Pain:** OR: 50-10 mg/6-8 h OR retard: 100-200 mg/12 h Rectal: 100 mg/6-8 h SC-IM: 50-100 mg/6-8 h Maximum dose: 400 mg/day	Dizziness, confusion, perspiration, postural hypotension, nausea, dry mouth	The association of a laxative may be necessary. Reduce dose in older people and renal failure Less drowsiness and constipation than codeine, but greater risk of interactions (SSRI, tricyclic antidepressants, triptanes, MAOIs, oral anticoagulants, bupropion, neuroleptics) Can be administered by SC route.
TRAMADOL + PARACETAMOL	Paxital® Pontalsic® Zaldiar®	Tab: 37.5/325 mg	**Pain:** OR: 75/650 mg/6-8 h (2 tab/6-8 h) Maximum dose: 8 tab/day	See tramadol	
TRANEXAMIC ACID	Amchafibrin®	Tab: 500 mg Ampoules: 500 mg	**Haemorrhage:** OR: 1-1.5 g/8-12 h IV,IM: 0.5-1 g/8-12 h	Nausea, abdominal pain, diarrhoea, myalgias, weakness, rhabdomyiolysis with myoglobinuria, thrombosis	
TRAZODONE	Deprax®	Tab: 100 mg	**Insomnia (above all associated with depression):** 25-100 mg at bedtime **Depression:** OR: 100-300 mg Maximum dose: 400 mg/day, older people 200 mg/day	Dry mouth, sedation, urinary retention, orthostatic hypotension, cardiovascular disturbances, priapism	Administered at night (sedative effect). Less anticholinergic, cardiovascular and extrapyramidal effects.
TRIAZOLAM	Halcion®	Tab: 0.125 mg	**Insomnia:** 0.125 mg at bedtime		Rapid action and short duration
SODIUM VALPROATE	Depakine® Depakine Crono® Milzone®	Tab: 150-200-300-500 mg Sachets: 500-1000 mg Phial: 300-400 mg	**Secondary prevention of convulsive crises:** OR 20-30 mg/kg/day divided into 2-3 doses	Nausea, diarrhoea, weight gain, thrombopaenia, hyperactivity, aggressiveness, ataxia, trembling, hepatopathy pancreatitis	
ZALEPLON	Sonata®	Tab: 5-10 mg	**Insomnia:** 5-10 mg at bedtime		Rapid action and short duration Conciliation insomnia

Drug	Trade-mark**	Presentation	Indications and dosage***	Most frequent adverse effects	Remarks
ZOLEDRONIC ACID	Zometa® Aclasta®	Phial: 4 mg	**Bone pain:** IV perfusion: 4 mg/100 ml in 15 minutes at least, every 3-4 weeks **Hypercalcaemia:** Solution for IV perfusion: 4 mg in 15 minutes minimum (diluted with 100 ml 0.9% sodium chloride or 5% glucosate)	Fever, pseudoinfluenza, nausea, anorexia, abdominal pain, diarrhoea, constipation, arthralgias, myalgias, anaemia	Precaution in cardiopaths and renal failure Maintain good hydration Maxillary osteonecrosis has been described (dental revision is recommended before treatment) Hospital use
ZOLPIDEM	Zolpidem GD Dalparn® Stilnox®	Tab: 10 mg	**Insomnia:** 5-10 mg at bedtime		Rapid action and short duration Conciliation insomnia
ZOPICLONE	Limovan® Siaten® Datolan® Zopicalma®	Tab: 7.5 mg	**Insomnia:** 7.5 mg at bedtime		Rapid action and short duration Conciliation insomnia

OR: oral route; SC: subcutaneous. IV. Intravenous. IM: intramuscular. SL: sublingual. Tab: tablets. Caps: capsules

* Use of SC route: not included in technical data sheet
** The list of trade-marks is not comprehensive
*** Some indications mentioned are not contemplated in the technical data sheet

Appendix 6. Subcutaneous drug administration in palliative care

Indications for use of subcutaneous route

The use of the subcutaneous route is indicated in those circumstances where the patient cannot take the medication orally or when the symptoms are not sufficiently controlled by this route. In practice, the situations where the subcutaneous route is considered as a first choice option are: uncontrolled nausea and vomiting, serious dysphagia, bowel occlusion syndrome that is not a surgical candidate, palliative sedation, unease, convulsions, and care in agony. Although not very frequent in daily practice, the situations that advise against the use of the subcutaneous route to administer drugs are anasarca, states of shock and severe coagulopathies.

Technique to use the subcutaneous route

The medication can be administered in two ways: in bolus or in continuous infusion using the devices (infusion pumps) that exist on the market. The latter are the best choice as the "bolus effect" is avoided and they permit the joint administration of mixtures of different drugs.

Infusion pumps can be elastomeric, mechanical or electronic depending on the mechanism used. Many of them also permit the administration of drugs in bolus if required (due to breakthrough pain, for example).

Necessary material

- Infusion pump
- Syringes
- 25 G syringe driver type needle
- Transparent dressing and adhesive strips
- Saline solution or water for injection
- Antiseptic solution (chlorhexidine, povidone-iodine)
- Gloves

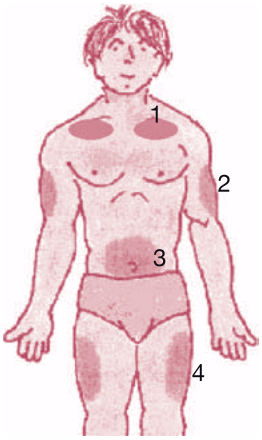
The procedure starts with the insertion of a 23-25 G metal needle syringe driver or a plastic catheter into the subcutaneous cellular tissue and securing it with a transparent adhesive dressing that permits seeing the puncture area.

The most frequently used anatomic locations are the infraclavicular anterior thoracic area, deltoideal area, the abdomen and the anteroexternal side of the thigh, avoiding areas with skin problems (figure 1).

It is advisable to periodically check the area where the syringe driver has been inserted to detect local problems (hardening or oedema, reddening, infection, haematoma) that may compromise the absorption of the medication or the accidental release of the syringe driver. The point of insertion of the syringe driver will be changed when local problems appear that may make absorption difficult. The administration in bolus with volumes of more than 2 ml will be avoided as this is more painful and favours the appearance of hardening and erythema, above all in the case of repeated injections.

Figure 1. **Recommended puncture areas for subcutaneous route**
(*modified and reproduced with the permission of Fisterra http://www.fisterra.com/material/tecnicas/parenteral/subcutanea.asp*)

1. Infraclavicular
2. Deltoideal
3. Abdomen
4. Thigh



Medication administered by subcutaneous route

Several drugs can be administered at the same time although their compatibility in one single device has not been well-established on many occasions.

Table 1. **Most commonly used drugs by SC route in PC**

Drug	Indications	Presentations
Morphine	Pain, dyspnoea	Amp 1 ml 1% = 10 mg Amp 1 ml 2% = 20 mg Phial 20 ml 2% = 400 mg
Butylscopolamine	Premortem death rattles, sialorrhoea, respiratory secretions, bowel obstruction	Amp 1ml = 20 mg
Midazolam	Convulsions, palliative sedation	Amp 3ml = 15 mg Amp 5 ml = 5 mg
Metoclopramide	Nausea and vomiting	Amp 2ml = 10 mg Amp 20 ml =100 mg
Haloperidol	Nausea and vomiting due to opioids, vomiting in the bowel obstruction, delirium	Amp 1ml = 5 mg
Levomepromazine	Anxiety / unease	Amp 1 ml = 25 mg
Dexamethasone	Multiple indications in PC	Amp 1 ml = 4 mg Amp 5 ml = 40 mg
Ketorolac	Pain, fever	Amp 1 ml = 10 mg Amp 1 ml = 30 mg
Octreotide	Bowel obstruction	Amp 1 ml = 0,05 mg Amp 1 ml = 0,1 mg Phial 5 ml = 1 mg
Tramadol	Pain	Amp 1 ml = 100 mg

Other drugs that have been used by SC route are: bupivacaine, buprenorphine, calcitonin, ceftriaxone, clonazepam, scopolamine, fentanyl, furosemide, granisetron, hydromorphone, hydrozycine, ketamine, methadone and ondansetron, among others.

Infusers

Infusers are devices especially designed to infuse the medication constantly and continuously. Its use permits the mixture of drugs and their simultaneous infusion by subcutaneous route. There are several types of infusers on the market: elastomeric (with ball mechanism), mechanical (with spring or syringe mechanism) and electronic (with peristaltic type mechanism). Many of them also permit the administration of drugs in bolus if required (due to appearance of breakthrough pain, for example).

The following variables must be taken into account when loading the infuser:

- The outlet flow measured in ml/h
- The autonomy time: one day, 5 days or 7 days, normally
- The total fill volume measured in ml, which is related to the above two parameters. Thus, the total fill volume of a one-day infuser with a outlet flow of 2.1 ml/h is 50 ml (2.1 ml/h x 24 h).

The cumulative volume of the drugs to administer is calculated with these reference variables and according to their presentation formats, completing the total capacity of the device with saline solution or water for injection.

Examples: a patient requires mg of morphic chloride, 5 mg of haloperidol and 30 mg of metoclopramide a day to control nausea and vomiting.. We have a 1-day elastomeric pump with an outlet flow of 2.1 ml/hour and a fill volume of 50 ml.

Preparation:

- 50 mg Morphine = 5 1-ml ampoules of 1% morphic chloride = 5 ml
- 5 mg Haloperidol = 1 1-ml ampoule = 1 ml
- 30 mg Metoclopramide = 3 2-ml ampoules = 6 ml

In all, the medication occupies a volume of 12 ml; the volume of saline solution we will use to fill the pump is 38 ml saline solution (50 ml total volume – 12 ml medication).

When the medication needs are known and stable, an infuser for several days can be used. In the above case, if we have a 5-day infuser with an outlet flow of 1.5 ml/h and a fill volume of 275 ml, the preparation would be done as follows:

- Morphine 50 mg/day = 250 mg/5 days = 25 amp 1% = 25 ml
- Haloperidol 5 mg/day = 25 mg/5 days = 5 amp = 5 ml
- Metoclopramide 30 mg/day = 150 mg/5 day = 15 amp = 30 ml

In this case the medication occupies a volume of 60 ml, so the volume of saline solution necessary to completely fill the device is 215 ml (275- 60 ml).

Compatibility of mixtures

- In our setting, the dilution is generally done with saline solution, as its tonicity is very similar to physiological solution, except for drugs such as diamorphine or cycline where dilution in water for injection is recommended (diamorphine is a widely used drug in Anglo-Saxon countries but it is not available in our setting). Water for injection has a lower risk of precipitation, so some sources recommend its use when making mixtures of several drugs (except when octreotide or ketamine are used); it is also advisable to dilute mixtures in order to reduce the risk of precipitation.
- Dexamethasone and ketorolac must not be mixed with other drugs.
- It is advisable to throw away any mixture that produces precipitates or solution turbidity.
- It is recommended not to mix more than three drugs due to the increased risk of precipitation of the resulting solution.

The most commonly used mixtures include morphine, butylscopolamine and midazolam, normally used in agony situations, and the mixture comprised of morphine, haloperidol and butylscopolamine, used for the palliative treatment of the bowel occlusion syndrome.

Table 2, modified from Porta *et al*., shows some of the mixtures of 3 compatible drugs used in clinical practice that include morphine. Information about the compatibility of mixtures can be consulted at http://www.pallcare.info/

Table 2. Compatible mixtures of three drugs that include morphine

Morphine	Haloperidol	Scopolamine (clorhydrate)
Morphine	Haloperidol	Butylscopolamine
Morphine	Haloperidol	Midazolam
Morphine	Haloperidol	Octreotide
Morphine	Butylscopolamine	Midazolam
Morphine	Scopolamine (clorhydrate)	Midazolam
Morphine	Metoclopramide	Midazolam
Morphine	Levomepromazine	Midazolam
Morphine	Levomepromazine	Scopolamine (clorhydrate)

This appendix has been prepared based on the following references:

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Appendix 7. Opioid dosage in pain

Approximate equivalence between opioids

The conversion factor is expressed as a fraction with respect to oral morphine or in mg with respect to a dose of 30 mg oral morphine:

Drug	Approximate equivalent dose (mg)*	Approximate Conversion Factor *
Oral Morphine	30 mg	1
SC, IM, IV Morphine	10-15 mg	2:1 a 3:1
Oxycodone	15 mg	2:1
Methadone**	variable	variable
Hydromorphone	6 mg	5:1
Codeine***	300-360 mg	1:10 a 1:12
Dihydrocodeine***	300-360 mg	1:10 a 1:12
Tramadol***	300	1:10

(*) The equivalent dose and conversion factors are only given as a guideline, so the response must be monitored when changing from one opioid to another.

(**) Methadone: marked difference among subjects between their plasma half-life, the analgesic power and the action duration.

(***) Little available information; according to other sources the conversion factor for codeine is 1:7.

Example: in a patient who takes codeine at a dose of 60 mg every 6 hours (= 240 mg/day), to change to morphine the conversion factor 240 mg/10 or 12 = 20-24 mg oral morphine oral per day is applied.

Dosage with oral morphine

- It is the opioid of choice.
- To adjust the dose it is recommended to start with immediate release tablets or oral morphine solution, at a dose of 5-10 mg/4 h to substitute an analgesic with less power (such a paracetamol), and at a dose of 10-20 mg or more to replace a weak opioid (such as codeine). The dose is gradually increased by 25-50% the daily dose (e.g. from 50 mg/day to 75 mg/day) until the symptoms are controlled. When the patient has been without pain for 2-3 days, it is recommended to change to retard release morphine (calculating the total daily dosage and administering it in two doses a day).
- Immediate release morphine rescue doses must always be given (15% the daily dose, that is 1/6).
- The need for more than three rescue doses a day means increasing the dosage of retard release morphine (25-50% of the daily dose).
- Another option is to start with retard release tablets, 10-20 mg/12 hours to replace analgesics such as paracetamol, and with 20-30 mg/12 hours to replace weak opioids, although this is not the most recommended solution.
- To change from oral route to SC route, the total dosage is divided into two doses.

Dosage with transdermal fentanyl

Fentanyl patches are useful when:

- Oral route is not adequate (patient's preferences, gastrointestinal disorders, swallowing problems).
- Morphine is not tolerated (constipation, drowsiness, confusion, etc.).
- There are problems of fulfilment.

Considerations:

- Patches are not appropriate in patients with unstable pain or with a marked irruptive component.
- Fentanyl is a powerful opioid.
- Its action is very slow-starting, meaning that the analgesic needs must be covered in the initial phase (12-15h).
- Its residual action persists up to 17 hours after removing the patch, which is a disadvantage in case of toxicity.

Dosage in patients with no prior treatment with opioids:

Treatment must begin with a patch of 25 micrograms/hour every 3 days, prescribing rescue with rapid release oral morphine (15% of the equivalent dose of morphine, that is 1/6) or oral transmucous fentanyl. If the pain is not controlled well or requires more than 3 rescue doses a day, the dosage is increased by 12-25 mcg/h, and so on and so forth until the efficient dosage is reached.

It is important to rotate the skin application areas, putting it on smooth, clean dry surface with little hair.

Dosage in patients previously treated with morphine:

- Calculate the analgesic needs of morphine of the previous 24 hours.
- Convert these quantities into the equianalgesic dose of fentanyl using the morphine to fentanyl conversion table (see conversion tables: the conversion table of the technical data sheet of fentanyl is more useful for high doses of opioids; the conversion table of the Therapeutic Prescription Guideline is also enclosed, as it is more practical for lower doses of opioids).
- There is also a rough rule that consists in calculating the fentanyl patch corresponding to half the daily dosage of oral morphine; and if high doses of morphine are required, the ratio will be the most conservative, one third; for example, if the patient needs 600 mg oral morphine the patch to be used will be «200» (two patches of «100»).
- It takes about 12 hours for the patch to have an effect. So, the last dose of retard morphine or three doses every 4 hours must be administered with the first patch, if the patient was treated with immediate release morphine.
- EXAMPLE: in a patient taking 60 mg morphine a day (with retard oral morphine administered in three doses), the equivalent would be a «25» fentanyl patch, which would be administered together with the last dose of 30 mg retard oral morphine.

Managing breakthrough pain with oral transmucous fentanyl (OT):

- Indicated only in breakthrough pain in patients receiving opioids.
- Their action is quick and short (15 minutes-4 hours).
- There is no correlationship between the maintenance dosage used and the efficient dosage of OT fentanyl.
- Dosage range: 200-1600 mcg.
- The right dosage for each patient is determined individually and it cannot be predicted based on the maintenance dosage of opioid, generally starting with 200 mcg. It is recommended to control the patient up to a dosage that offers adequate analgesia and then use one dose unit per episode of breakthrough pain («efficient dosage »). If more than 5 units are required (maximum dosage): adjust baseline treatment.

To withdraw the fentanyl patches and change to morphine:

- After the patch has been removed, a reserve remains that continues to release the drug for about 17 hours.
- Only rescue medication is recommended for use during the first 12-24 hours, changing afterwards to retard oral morphine. Watch for possible signs of toxicity.
- If an infusion pump is going to be used, wait at least 12 hours and then use a reduced dosage for the next 12 hours.
- EXAMPLE: In a patient with «25» fentanyl patches, who requires a rescue dose (for example, a dose of 15 mg immediate release morphine), the total daily dose of morphine will be = 90 mg (equivalent to «25» fentanyl) + 15 mg morphine = 105 mg retard oral morphine (administered in two doses). If a change is going to be made to SC route: the oral dosage is divided into two doses (105/2 = 52.5mg/día).

Fentanyl in patients in agony phase:

In the case of patients in agony phase with uncontrolled pain and who cannot take medication orally, it is recommended:

- To continue to change the fentanyl patches every 3 days.
- If additional analgesia is required, also use morphine by subcutaneous route.

Conversion table from oral morphine oral to transdermal fentanyl

Oral morphine 90 mg/day = «25» fentanyl patch
Oral morphine 180 mg/day = «50» fentanyl patch
Oral morphine 270 mg/day = «75» fentanyl patch
Oral morphine 360 mg/day = «100» fentanyl patch

Source: Therapeutic Prescription Guideline. Ministry of Health and Consumer Affairs.

Conversion table from oral morphine to transdermal fentanyl

Oral morphine 24-hours (mg/day)	Dose of transdermal fentanyl (micrograms/hour)
<135	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

Source: Technical Data Sheet.

Dosage with transdermal buprenorphine

Considerations:

- It is not the opioid of choice, as there are very few studies and limited experience.
- It has an analgesic ceiling.
- It is not appropriate for acute pain.
- Removal of the patch: as a general rule no other opioid must be administered in the 24 hours after the removal of the buprenorphine patch.

Dosage in patients without prior treatment with opioids:

The treatment must be started with a 35 mcg/h patch every 3 days. If the analgesia is insufficient after 72 hours, the dosage must be increased to two patches of the same concentration or change to the next concentration. If rescue medication is required, the criteria will be for sublingual buprenorphine (1 or 2 0.2 mg sublingual tablets every 24 hours apart from the patch). If it is necessary to add between 0.4 and 0.6 mg sublingual buprenorphine (2-3 tablets) the next patch concentration must be used.

Dosage in patients previously treated with morphine:

- Calculate the analgesic needs of the previous 24 hours.
- Convert these quantities into the equianalgesic dose of buprenorphine, using the morphine to buprenorphine conversion table.
- Use a criterion of rescue medication, using sublingual buprenorphine (1 or 2 0.2 mg sublingual tablets every 24 hours apart fmo the patch).

Conversion table from oral morphine oral to transdermal buprenorphine

Oral morphine 30-60 mg/day = 35 mcg/h buprenorphine patch
Oral morphine 90 mg/day = 52.5 mcg/h buprenorphine patch
Oral morphine 120 mg/day = 70 mcg/h buprenorphine patch
Oral morphine 240 mg/day = 2 70 mcg/h buprenorphine patch

Dosage of oxycodone

- It is not the opioid of choice.
- 10 mg oral oxycodone are equal to 20 mg oral morphine.
- In patients who have not taken opioids, the initial dose is 10 mg every 12 hours. The dose must be adjusted, with increases of 25-50%. The need for rescue medication more than twice a day means that the dose must be increased.

The following references have been used to develop this appendix, apart from the bibliography of the relative chapter of the CPG:

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Appendix 8. Glossary and abbreviations

Glossary

AGREE (Appraisal of Guidelines, Research and Evaluation for Europe)**:** International initiative to facilitate the design and evaluation of clinical practice guidelines.

Agony: State that precedes death in those illnesses where life gradually expires. It is characterised by the appearance of a general physical deterioration, which is usually quickly progressive, showing an increase of weakness, deep depression and reduction of the alert level, with the subsequent increase of the number of hours in bed, reduction of consumption and disturbance of vital signs; progressive tendency to hypotension, tachycardia and oliguria, with perception of imminent death by the patient, family and team of health professionals.

Autonomy (principle of): It considers that all people have the right to freely dispose and to act in agreement with the principles that have governed their lives.

CAMPAS-R: A tool used to prospectively monitor symptoms in patients under home palliative care. Using visual analogue scales it measures the severity and interference of: pain, nausea, vomiting, constipation, fatigue, dyspnoea, anxiety and depression..

Cochrane Library: Database on effectiveness produced by the Cochrane Collaboration, comprised among others of the original systematic reviews of this organisation.

Cohort study: This consists in the follow-through of one or more cohorts of subjects with different degrees of exposure to a risk factor, in whom the appearance of the disease or condition studied is measured.

Confidence interval: This is the interval within which the real magnitude of the effect (never known exactly) is found with a pre-established degree of certainty or confidence. The «90% confidence interval» (or «9% confidence limits») is often mentioned. This means that the real value would be found within that interval in 95% of the cases.

Control-case Study: Study that identifies people with a disease (cases), for example lung cancer, and compares them with a group without the disease (control). The relationship between one or several factors (for example tobacco) relating to the disease is examined, comparing the frequency of exposure of this or other factors between the cases and the controls.

Embase: European database (Dutch) produced by Excerpta Medica with clinical and pharmacological medicine content.

Ethics Committee: Any consultant and interdisciplinary commission at the service of the professionals and users of a health institution, created to analyse and advise on the solution of possible ethical conflicts that arise as a result of healthcare work and whose objective is to improve the quality of such health care.

Euthanasia: The acts whose aim is to deliberately terminate the life of a patient with a terminal or irreversible disease, whose suffering is intolerable and on the express request of this person.

Euthanasia, active, positive or occision: These are actions aimed at deliberately producing the death of a patient who is suffering intolerably.

Euthanasia, passive, negative or lenitive: This is the omission or suspension of therapeutic attitudes that prolong the life of a patient who is suffering from a terminal or irreversible disease. This is what is called limitation of therapeutic effort today.

Focal group: This is a conversational technique to obtain information in qualitative research, and as such it responds to the intended sampling criteria, flexibility and circularity typical of this methodology. It consists of a group interview where the participants –between 5 and 10- set out and discuss their appraisals around a theme proposed by the researcher-moderator. The script is open or semi-organised and everything discussed in the group is recorded and transcribed for subsequent analysis.

Futility: Characteristic attributed to a medical treatment that is considered useless because its objective to provide the patient with a benefit is highly likely to fail and because the rare exceptions are appraised as risky and, therefore, cannot be considered as an argument to make a clinical decision. This definition has been considered to apply to two aspects: one, the high likelihood of failing (quantitative); another, the patient's benefit (qualitative). Another definition; any treatment that does not satisfy the expectations placed on it or is simply inefficient.

Heterogeneity: See «Homogeneity».

Homogeneity: It means «similarity». It is said that two or more studies are homogeneous when their results do not vary more than what can be expected by chance. The opposite to homogeneity is heterogeneity.

Limitation of therapeutic effort: The decision to restrict or annul some type of measures when a disproportion between the therapeutic ends and means is perceived, with the aim of not falling into therapeutic obstinacy.

Medline: Predominantly clinical database produced by the US National Library of

Medicine, available in CD-Rom and Internet (PubMed).

Meta-analysis: This is a statistical technique used to integrate the results from different studies (diagnostic test studies, clinical trials, cohort studies, etc.) in one single estimator, placing more importance on the results of larger studies.

NICE: This forms part of the NHS (British National Health Service). Its role is to provide physicians, patients and the public in general with the best available evidence, mainly by way of clinical guidelines.

NNT/NNH: This is a measurement of the efficiency of a treatment: the number of people needed to treat (NNT) with a specific treatment to produce, or avoid, an additional event. Likewise the number needed to harm (NNH) is defined to assess undesirable effects.

Odds Ratio (OR): This is a measurement of the efficiency of a treatment. If it is equal to 1, the effect of the treatment is no different to the effect of the control. If the OR is more (or less) than 1, the effect of the treatment is greater (or lesser) than the effect of the control. Note that the effect that is being measured can be adverse (e.g. death, disability) or desirable (e.g. stop smoking).

Proportionality (criterion of): This is the analysis between the positive effects of the treatment or of the diagnosis and the negative effects –such as the burdens that the side effects may represent or the pain that may be generated-. It is a criterion of best clinical practice that the professional has to make. The criterion of proportionality will help know if the medical or surgical treatment proposed provides greater benefit for the patient.

Qualitative research: This is a methodology that comprises a plurality of theoretic currents, methods and techniques and it is basically characterised by studying the phenomena in their natural context, trying to find their meaning or interpretation based on the meanings that

people give to them. Empiric materials (interviews, observations, texts, etc.) that can best describe both the routine and problematic situations and what these mean in the individuals' lives are used.

Quality of living: The subjective perception that an individual has of living in decent conditions. It responds to the aspirations and to the maxims that a person wants for himself or herself.

Randomised clinical trial: It is a study design where the subjects are randomly assigned to two groups: one (experimental group) receives the treatment that is being tested and the other (comparison and control group) receives standard treatment (or at times a placebo). Both groups are monitored to observe any differences in the results. The treatment efficiency is thus evaluated.

Relative Risk (RR): The quotient between the rate of events in the treatment and control group. Its value follows the same interpretation as the OR.

Rule of Clinical Prediction: This is a clinical tool that quantifies the individual contribution of several components of the clinical history, physical examination and laboratory results or other variables on the most likely diagnosis, prognosis or most probably response to a treatment in a specific patient.

SIGN: Scottish multidisciplinary agency that prepares evidence-based clinical practice guidelines as well as methodological documents on the design of these guidelines

Specificity: This is the proportion (percentage) of really healthy people who have a negative test result. That is, the proportion of real negatives.

Suffering: This is a complex negative cognitive and affective state, characterised by the feeling that the subject has of his or her integrity being threatened, the feeling of impotence before this threat and the exhaustion of personal and psychosocial resources that would enable him or her to cope with it.

Systematic Review (SR): This is a review where the evidence on a topic has been systematically identified, appraised and summed up in agreement with some predetermined criteria. It may or may not include the meta-analysis.

Transverse-Descriptive Study: This is a study that describes the frequency of an event or an exposure at a given time (single measurement). It permits the examination of the relationship between a risk factor (or exposure) and an effect (or results) in a defined population and at a given time (a cut). Also called prevalence studies.

The terms listed with methodological aspects are based on the CASPe glossary (critical appraisal skills programme in Spain), at http://www.redcaspe. org/homecasp.asp.

Abbreviations

ACEI	Angiotensin converter enzyme inhibitor
ADL Scale	Activities of Daily Living
AECC	Spanish Cancer Association
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
BPI	Brief Pain Inventory
BPQ	Brief Pain Questionnaire
BZD	Benzodiazepines
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CARING Scale	Cancer, Admissions, Residence in a nursing home, Intensive care unit, Noncancer hospice Guidelines
CAT	Computerised axial tomograph
CCI	Congestive heart failure
CDS	Cancer Dyspnoea Scale
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CPG	Clinical practice guideline
CRQ-D	Chronic Respiratory Questionnaire Dyspnoea Subscale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ECOG Scale	Eastern Cooperative Oncology Group
EGG	Electrocardiogram
EOL	End-of-life phase
EORTC QLQ-C15-PAL	European Organisation for Research and Treatment of Cancer questionnaire for cancer patients in palliative care
ESAS	Edmonton Symptom Assessment System
FAST Scale	Functional Assessment Staging
FEV	Forced expiratory volume
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HES	Healthcare Ethics Committee
HCSE	Home Care Support Equipment
IASP	International Association for the Study of Pain
ICSI	Institute for Clinical Systems Improvement
ICU	Intensive care unit
IM	Intramuscular
INR	International Normalised Ratio
IV	Intravenous

LW	Living wills
MANE	Morrow Assessment of Nausea and Emesis
MBO	Malignant bowel obstruction
MDAS	Memorial Delirium Assessment Tool
MELD	Model for End Liver Disease
MSAS Scale	Memorial Symptom Assessment Scale
MSCCM	Malignant Spinal Cord Compression
NHPCO	US National Hospice Palliative Care Organization
NMR	Nuclear magnetic resonance
NRS	Numeric Rating Scale.
NSAID	Non-Steroidal Anti-Inflammatory Drugs
N SRI	Noradrenaline serotonin reuptake inhibitors
NYHA	New York Heart Association
PACSLAC Scale	Pain Assessment Checklist for Senior with Limited Ability to Communicate.
PADES	Home care programme and support teams
PaP Score	Palliative Prognostic Score
PC	Palliative Care
PG	Preliminary Guidelines
PHC	Primary Health Care
PI	Preliminary instructions
PPI	Palliative Prognostic Index
PU	Pressure ulcers
RCOPE	Brief Measure of Religious Coping
RCP	Respiratory compensation point
RCT	Randomised clinical trial
SBI	System of Belief Inventory
SC	Subcutaneous
SCC	Spinal Cord Compression
SCS	Spinal Cord Compression Syndrome
SDS	Symptom Distress Scale
SEMP	Self-expanding metal prostheses
SGRQ	St George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SSRI	Selective Serotonin Reuptake Inhibitors
SVCO	Superior vena cava obstruction
TIPS	Transjugular intrahepatic portosystemic shunt
TDA	Tricyclic antidepressants
VAS	Visual Analogue Scale
WHO	World Health Organisation

Appendix 9. Declaration of Interests

Mila Arrieta, Laura Balagué, Eduardo Clavé, Larraitz Egaña, Arritxu Etxeberria, Jesús García, Juan Luis Merino, Manuel Millet, Rafael Rotaeche and Juan José Sagarzazu have completed the absence of conflict of interest statement. Ana Bañuelos has received support from the pharmaceutical industry to attend congresses. José María Salán has received support from the Aventis and Mundipharma laboratories to attend congresses.

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Jose Manuel Agud, Xavier Gómez-Batiste, Socorro Lizarraga and Jaime Sanz have not completed the conflict of interest statement.

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