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## Palliative Care in General Practice

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*"You matter because you are you. You matter to the last moment of your life, and we will do all we can to help you not only to die peacefully, but also to live until you die."*  
Dame Cicely Saunders, St. Christopher's Hospice

### 1. Introduction

The doctor-clown Patch Adams argued that our health care system should not treat the disease, but the patient, in an approach "patient-centered" rather than "disease-centered". Palliative care is a holistic, patient-centered, and culturally sensitive approach to care. According to the Nobel Prize winner Rita Levi Montalcini, "it's better to add life to days, rather than days to life". For those who are dying a good quality of their last days of life is more important rather than prolong unnecessarily the days of the agony. Palliative care focuses on relieving suffering and achieving the best possible quality of life for patients and their family caregivers.

Palliative medicine (from the Latin word "pallium" for mantle, as a synonym of protection) takes care of the patients (and their boundary) rather than the disease(s) that afflicts them.

Palliative care involves not only the patients themselves, but also their families and communities. In practice, palliative care integrates two essential components of care. One is the control of symptoms and pain, the other are the interventions to meet the psychological, social, and spiritual needs of the patient and the family. The palliative care framework calls for varied combinations of these two components to be provided over the full course of the illness, from diagnosis to death, and through the bereavement of family members.

The National Consensus Guidelines for Palliative Care (2011) state the goals of palliative care are to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies.

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The role of the General Practitioner (GP) is central to community palliative care. Good liaison between the different professionals involved in a patient's care is extremely important for patients in palliative care. In cases where GPs have previously been dissatisfied with palliative services, this may be seen as a barrier to referral when caring for other patients (Bajwah, 2008). With a GP's longitudinal knowledge of patients, and the likelihood that they have shared the journey of the final illness with the patient, it should be beyond dispute that there should be a central role for general practice in palliative care. Physicians must adopt a vision that takes into account the effects that diseases are having not just on patients but also on patients' caregivers and loved ones, a systemic vision. (Emanuel et al, 2011).

The essence of the doctor-patient relationship makes family physicians ideally suited to provide care palliative and end-of-life. Cassell, (1982), has defined that this relationship is the very means to help relieve suffering.

In order to develop the wide term of palliative care, we would like to consider both advance care planning, aid with decision making and clinical care management.

## 2. Palliative care in general practice: Why is it so important?

Mr Ralph Smith is a man 74 years old who has suffered from a pulmonary cancer for about 15 months, treated with chemotherapy and radiotherapy on the chest. He lives with his wife (72 y.o.), hemiplegic for an ictus, and a daughter (40 y.o.), who works as a primary teacher. Recently he has developed a metastatic localization in the lumbar spine with increasing pain, severe limitation to movement and urinary retention. The general conditions are quite compromised (Karnofsky Index < 40) with a very poor prognosis (less than 3 months). Ralph refused the antalgic radiotherapy on the lumbar spine proposed by the oncologist. His family doctor proposed him a palliative care program by the Home Palliative Care Team.

Palliative care, with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services. However, palliative care has traditionally been delivered late in the course of disease to patients who are hospitalized in specialized inpatient units or as a consultative service for patients with uncontrolled symptoms. Previous studies (Morita et al, 2005; Zimmermann et al, 2008) have suggested that late referrals to palliative care are inadequate to alter the quality and delivery of care provided to patients with cancer. To have a meaningful effect on patients' quality of life and end-of-life care, palliative care services must be provided earlier in the course of the disease (Temel et al, 2010).

To date, evidence supporting a benefit of palliative care is sparse, with most studies having notable methodologic weaknesses, especially with respect to quality-of-life outcomes (Zimmermann et al, 2008). One study showed that Project ENABLE (Educate, Nurture, Advise, Before Life Ends), a telephone-based, psychoeducational program for patients with advanced cancer, significantly improved both quality of life and mood (Bakitas et al, 2009) .

Another recent study (Temel et al, 2010) showed that early outpatient palliative care for patients with advanced cancer can alter the use of health care services, including care at the

end-of-life. Early introduction of palliative care led to less aggressive end-of-life care and showed greater documentation of resuscitation preferences in the outpatient electronic medical record, an essential step in clarifying and ensuring respect for patients' wishes about their care at the end-of-life (Walling et al, 2008). Less aggressive end-of-life care did not adversely affect survival.

Given the trends toward aggressive and costly care near the end-of-life among patients with cancer, timely introduction of palliative care may serve to mitigate unnecessary and burdensome personal and societal costs (Emanuel et al, 2002; Earle et al, 2008; Sullivan et al, 2011).

Morrison and Meier (2004) articulate five broad areas of skills that form the core of palliative medicine: physician-patient communication; assessment and treatment of symptoms; psychosocial, spiritual, and bereavement care; coordination of care. This involves defining practice standards, responsibility for educational development and implementation, research in partnership with the academy, and program and systems needs.

In palliative care, the dying is seen as having an important role, complete with tasks and expectations, that is different from the sick role when recovery is expectable (Davies, 2009). The goal is not to prolong or shorten life; rather, the process of dying is to be freed of as much unnecessary suffering as possible. The inevitable dimensions of suffering that accompany dying and death can be soothed by finding meaning and purpose in the life lived and enhancing quality of life and quality of the dying process (Emanuel et al, 2011).

Palliative care is a paradigm of excellence for the generalist. The specific nature of palliative care allows GPs to showcase the strength of a generalist approach. This 'excellence' manifests as a creative tension between evidence-based biomedical care, a patient-centered approach and the more traditional role of 'healer'. GPs think and reflect around patient stories, rather than the abstraction of data to achieve best practice care (Eti & Heidelbaugh, 2011).

Patients repeatedly emphasize the importance of the role of a family physician with whom they have had close ties over the years, and for this role to continue through the palliative stages of life (Emanuel et al, 2007). Physicians must adopt a systemic vision, a vision that takes into account the effects that diseases are having not just on patients but also on patients' caregivers and loved ones (Emanuel et al, 2011). The family physician is also well positioned to address the concerns of the patient's loved ones and assist in coping with grief, as these persons are often patients in the physicians' practice (Lehman & Daneault, 2006).

An in-depth understanding of suffering in those who are seriously ill, and responding to it, is a fundamental role of primary care. Family physicians have the capacity to stay available and involved in care in a way that is reassuring to patients and alleviates patient suffering.

The primary care physicians often must deliver the bad news, discuss the prognosis, and make appropriate referrals. When delivering bad news, it is important to prioritize the key points that the patient should retain. Physicians should assess the patient's emotional state, readiness to engage in the discussion, and level of understanding about the condition. When discussing prognosis, physicians should be sensitive to variations in how much information patients want to know. The challenge for physicians is to communicate prognosis accurately without giving false hope. Physicians also must be aware of how cultural factors may affect

end-of-life discussions. Sensitivity to a patient's cultural and individual preferences will help the physician avoid stereotyping and making incorrect assumptions.

Primary care physicians have the opportunity to maintain long-term, trusting relationships with patients and are well positioned to discuss difficult issues such as incurable disease or terminal illness (Ngo-Metzger et al, 2008).

A good primary palliative care is essential, as it allows patients to remain at home as long as possible. It is known that most patients wish to do so and would eventually prefer to die at home among family and friends (Marieke et al, 2007).

A systematic review of studies (Daneaul & Dion, 2004) found that, overall, the majority of the general population as well as patients and caregivers would prefer to die at home, but the findings varied considerably by study, with the percentage of people preferring to die at home ranging from 25% to 100%.

Several studies have repeatedly shown that many terminally ill patients prefer the option of a death at home (Watson, 2008).

However there can be profound shifts in patient and caregiver preference for location of death as the illness progresses. Hinton (1994) found that the preference for a home death changed from 90% initially to 50% as death approached (Higginson & Sen-Gupta, 2000).

Most GPs testify to this being one of the more difficult, but most satisfying, parts of their job. Survey results of different populations vary considerably with regard to preference for home as the location of death (Davies & Higginson, 2004).

Helping patients die with dignity and with minimal distress has been one of the most fundamental aspects of medicine, and over the past 50 years specialistic palliative care services have increasingly worked with general practice to develop more advanced knowledge and skill than ever before.

The European Association of Palliative Care conducted a study, begun in 2003, that evaluated the situation of palliative care through Europe. A report with quantitative and qualitative data was prepared for 43/52 participating countries. In table 1 different organizational models, (Hospital based, Hospice and Home care) in European countries are shown. Iceland is at the first place with a rate of 20 service for million inhabitants, equally distributed as a hospital model or home care assistance.

Different models of service delivery have been developed and implemented throughout the countries of Europe. UK, Germany, Austria and Belgium have a well-developed and extensive network of hospices. Day Centres are a development that is characteristic of the UK with hundreds of these services currently in operation. The number of beds per million inhabitants ranges between 45-75 beds in the most advanced European countries, to only a few beds in others. The model for mobile teams or hospital support teams has been adopted in a number of countries, most notably in France (Centeno, 2007).

Italy and many other countries as Hungary, Bulgaria, Poland, Slovenia, etc. have preferably developed a Home care model based on a multidisciplinary team which include General Practitioners.

Rank	Country	Total Services/ Million Inhabitants	Hospital Support and Unit /Hospice	Home care	First Opioid used
1	Iceland	20,3	50 %	50 %	Morphine
2	United Kingdom	16,0	61 %	39%	Morphine
3	Belgium	11,6	88%	12%	Fentanyl
4	Poland	9,5	36%	64%	Morphine
5	Ireland	8,9	61%	39%	Morphine
6	Luxemburg	8,8	50%	50%	Fentanyl
7	Netherlands	8,5	100%	0%	NA
8	Armenia	8,1	67%	33%	Morphine
9	France	7,8	82%	18%	NA
10	Norway	6,7	97%	3%	Morphine
11	Austria	6,4	67%	33%	Fentanyl
12	Spain	6,0	47%	53%	Fentanyl
13	Bulgaria	5,5	39%	61%	Morphine
14	Switzerland	5,1	63%	37%	NA
15	Finland	5,0	62%	38%	Morphine
16	Hungary	4,3	35%	65%	Morphine
17	Germany	3,9	91%	9%	Morphine
18	Italy	3,8	36%	64%	Fentanyl
19	Israel	3,7	46%	54%	Oxycodone
20	Slovenia	3,6	29%	71%	Morphine
21	Moldova	3,3	15%	85%	Morphine
22	Denmark	3,3	72%	28%	Morphine
23	Cyprus	3,2	50%	50%	Morphine
24	Macedonia	2,9	67%	33%	Morphine
25	Malta	2,6	100%	0%	Morphine

NA: not available

Table 1. Palliative Care Specific Resources in Europe (Modified from EAPC, 2006)

However palliative care is still perceived by most physicians and patients as a waiver to care and a sentence to death. For these main reasons negative myths about palliative care have developed (Table 2).

These often are common barriers to the adoption and effectiveness of palliation in Primary Care. Health Systems should invest in improving the quality of Palliative Home Care to get an assistance really focused on the needs of the patient and his boundary. And it is fundamental to invest on physicians' communication skills.

Negative Myths	Palliative Care (PC) opportunities
PC means that doctors have given up on a patient.	When PC is proposed, it means that the healthcare team has realized that the disease is not curable and that death can't be avoided: PC offers the chance to live out the remaining days as comfortably as they can be, with the care of experts in end-of-life care.
PC means no more treatment.	When a PC team takes over the care of a patient, treatment doesn't automatically stop. Treatment and therapies can continue, but they have a different goal.
PC is only for people with cancer.	PC is offered to anyone with an end-stage of a chronic or terminal illness. Many people who receive PC can have AIDS, heart disease, COPD, multiple sclerosis, muscular dystrophy, and many other fatal illnesses.
PC is only for old people.	Many children are diagnosed with terminal illnesses. They may be born with a birth defect, such as a heart defect, or a disease that will cause them to die as a child or they may develop a terminal illness later on in their childhood.
PC means the patient is very close to death.	When someone is transferred to the PC team, they may die within days or weeks, or they may live for considerably longer. PC isn't offered according to the amount of time left.
In PC the use of narcotics or opioids is a type of euthanasia.	PC is not euthanasia. If the disease cause severe pain, the use of narcotics or opioids is useful to control the pain, but only if patient needs it and only at the dosages he needs it. The goal of PC isn't to help the patient to die, but, on the contrary, to make him as comfortable as possible during the end-of-life period.
PC can be given only in the hospital.	PC services are offered in many communities. Care at end-of-life can be given in a hospital, stand-alone residence, or at home, depending on the resources available.
PC reduce the family role.	One of the benefits of PC is that it's not only for the dying person. The PC team cares for the dying patient and his or her family and friends. The care at the end-of-life isn't just about physical comfort, but it's about emotional and psychological support for everyone who loves and is part of the life of the dying patient.
PC reduce the auto-control of the patient.	PC is a specialty in medicine. A patient in PC is consulted and is part of the team for as long as him or her is able to be ( <i>see also the paragraph on ACP</i> ).

Table 2. Negative Myths of Palliative Care (PC)

### 3. Doctor–patient relationship and patient-centered communication

*Mrs White Claire, a woman 40 years old, with two adolescent sons, is affected with a breast cancer with multiple liver, bones and brain metastases. Her mother died at 33 for breast cancer. She is currently receiving home care with opioids for bone pain. Her husband, John, requires to their GP a hospice admission for the appearance of a deep venous thrombosis in the right leg. At the admission the leg is edematous but not sore. The hospice doctor says to John that the general conditions are very compromised and the Claire prognosis is very poor (few days). He proposes not him initiate therapy with low molecular weight heparin, but to provide only supportive therapy. John is distressed and confused, he would like to counsel with their family doctor.*

The patient–doctor relationship is an important concept in health care, especially in primary care. One of the main competences required to the General Practitioner (GP) in the field of palliative care is to establish a good relationship both with the patient, the family and the other health care professionals engaged in the care process. In order to provide high quality assistance, effective communication between patients and health care providers is an essential element.

The clinicians need establish a therapeutic relationship based on trust and mutual respect with patients who often access a great deal of medical information, come from culturally diverse, have varying levels of social support, and confront the existential and spiritual aspects of dying, all while trying to access complicated health care systems (Foley & Gelband, 2001; Hewitt & Simone, 1999).

The primary care physicians form the backbone of an integrated team by providing an unbiased medical perspective and continuity during a stressful disease course, supporting patients and their families through emotional ups and downs, negotiating or mediating decisions, monitoring for complications, and providing perspective on the illness (Parker et al, 2001).

Despite around the 50-90% of the patients want to be informed about the diagnosis, the prognosis, the medical treatments and the side effects, even though it is a diagnosis of terminal phase, a relevant number of physician tends to hide unpleasant truths. In fact, patients affected by neoplasia with higher probabilities of being cured are usually informed more correctly and completely than patients affected by advanced disease (D'Errico & Valori, 2011).

When a patient and his/her physician enter into end-of-life discussions, each brings individual cultural backgrounds and values, which influence the discussions. Although understanding cultural norms is important, physicians must be careful to avoid stereotyping patients based on their culture (Kagawa- Singer et al, 2001).

The stress of disease and its treatment are often associated with intense negative emotions: sadness, fear, and anger. Though physicians often cannot “fix” the causes of these emotions, empirical studies indicate that providing emotional support ameliorates distress. Patients feel emotionally supported when their doctor shows care for them as a person, by spending enough time with them, allowing them to ask questions, and listening to their concerns (Wenrich et al, 2001).

The physicians should assess how much information to provide using patient-centered communication. After assessing the patient's readiness to receive prognostic information, the physician should focus on communicating the prognosis without giving false hope (Back et al, 2003). Though many clinicians equate honesty about a poor prognosis with destroying hope, healthy coping continually generates hope, even in difficult life situations. Even under situations of severe stress, positive emotions are prominent, and are an integral part of the coping process (Meier et al, 2001).

An American study described patients' hopes for a good death: freedom from pain and other symptoms, clear decision making, preparation for death, having a sense of completion, contributing to others, affirmation of the whole person, being at peace with God, being in the presence of family, being kept clean, and trusting one's physician (Steinhauser et al,



2000). Maintaining hope is essential to patients and their families at the end-of-life (Clayton et al, 2005; Shiozaki et al, 2005).

Retrospective studies (Ptacek et al, 2001; Salander, 2002; Wenrich et al, 2001) identified what patients want when hearing bad news. They prefer to have: bad news discussed in person, and in a private, quiet place; a physician who is able to communicate their diagnosis, prognosis, and treatment options clearly; full attention of the physician; time to ask questions; and to be given informations about how the diagnosis will affect their life (Back et al, 2008).

The Evidence-based recommendations and the best practices on the communication of bad news are summarized in box 1:

- Find a comfortable and private place to talk;
- Ask whether the patient would like to have others present;
- Minimize interruptions;
- Assess the patient's understanding of the situation;
- Let the patient know explicitly that bad news is forthcoming;
- Provide information honestly and in simple language;
- Give time for questions;
- Encourage patient to express emotions and respond empathically;
- Check understanding;
- Arrange a clear follow-up plan.

Box 1. Best practice for communicating bad news (adapted from Back et al, 2008).

The goals of care change as the disease progresses. At each stage, the physician should help the patient create realistic, achievable goals and hopes. Focusing on stage-specific goals and hopes can prevent over- and under-treatment while relieving the patient's psychological distress (Block, 2006).

Breaking bad news, particularly discussing prognosis, requires a combination of disease-specific biomedical knowledge and excellent communication skills (Back & Arnold, 2006).

Therefore, recommendations have been developed to help physicians appropriately deliver bad news, as reported in box 2:

- It is important for physicians to assess the patient's level of understanding about the disease and expectations for the future.
- It is important for the physician to assess how much information the patient wants to know and to tailor the discussion appropriately.
- The primary care physician should remain involved with patient care during the early, middle, and late stages of disease.
- Physicians should avoid phrases and words that can be misconstrued by the patient and lead to negative interpretations such as abandonment and failure.
- During end-of-life communication, physicians should assess and be sensitive to the patient's cultural and individual preferences.

Box 2. How to communicate bad news: recommendations for physicians (adapted from Ngo-Metzger et al, 2008)

Frequently, preparing the caregivers for the patient's death is not a main focus of communication (Rabow et al, 2004). Usually the family of a terminally-ill patient prefers that diagnosis is hidden to its loved one. This behaviour can be seen as a psychological defense system through which the patient's relatives face their own anxiety towards death. That is why the GP should also help the family members to understand what are the advantages of a frankly based relationship and what are the risks of a reticent and not honest relationship (D'Errico & Valori, 2011).

Observational studies (Steinhauser et al, 2001; Hebert et al, 2006) suggest that inadequate information and unpredictable situations might contribute to caregiver uncertainty, which is associated with poorer health outcomes for the caregiver himself. On the contrary, other studies demonstrate that when the caregivers perceive that their questions have been answered, they experience fewer depressive symptoms, fewer economic and other burdens, and improve their satisfaction and quality of life (Valdimarsdottir et al, 2004).

Knowledge about factors that hinder or facilitate the communication between GPs and patients in palliative care is needed in order to improve the quality of the palliative care itself and the life quality of the patients (Slort et al, 2011).

The most frequently reported barriers for GP-patient communication are:

- the GPs' lack of time;
- the patients' ambivalence or unwillingness to know about the prognosis;
- the GPs not talking honestly about the diagnosis or prognosis.

The most frequently reported facilitating factors are:

- the availability of the GPs,
- longstanding GPs-patient relationships,
- GPs showing commitment, being open and allowing any topic to be discussed,
- being honest and friendly,
- listening actively and taking patients seriously,
- taking the initiative to talk about end-of-life issues,
- not withholding information,
- negotiating palliative care options,
- being willing to talk about the diagnosis and prognosis, preparation for death, the patient's psychological, social and spiritual issues and the patient's end-of-life preferences.

In conclusion give dignity, space and attention to the communication are essential steps that need to be undertaken by a GP that recognizes a correct relationship with the patient as one of his main means of care and essential for a better advance care planning.

#### **4. Advance care planning**

Advance care planning (ACP) is a process that can support individual autonomy with respect to health care choices throughout the course of a life-threatening illness and at the end-of-life. Advance directives (ADs) are documents enabling capable individuals to plan for care in the case of their own incapacity.

The Institute of Medicine (cited by Emanuel et al, 2011) defines ACP as “not only the preparation of legal documents but also discussions with family members and physicians about what the future may hold for people with serious illnesses, how patients and families want their beliefs and preferences to guide decisions (including decisions should sudden and unexpected critical medical problems arise), and what steps could alleviate concerns related to finances, family matters, spiritual questions, and other issues that trouble seriously ill or dying patients and their families”.

As such, ACP is a process not a single event with the goal of learning about both what patients want and what they do not want for themselves in the future.

ACP includes (National Hospice and Palliative Care Organization, 2011):

- Getting information on the types of life-sustaining treatments that are available;
- Deciding what types of treatment one would or would not want should one be diagnosed with a life-limiting illness;
- Sharing personal values with loved ones;
- Completing advance directives to put into writing what types of treatment one would or would not want should one be unable to speak for itself.

A systematic review on the emotional impact of discussions about end-of-life decisions showed that the patients involved experienced positive benefits from the process (Song, 2004). Hypothetical benefits of ACP reported in the literature include increased inclusion of patient preferences for health care, more informed decision making, decreased pain and suffering, reduced costs and use of life-sustaining treatments, and improved patient and family satisfaction with care (Royal College of Physician, guideline 2009).

Another review (Knops et al, 2005) identified three domains of patient concern that are relevant for advance care planning conversations:

- feelings about the disease
- feelings about suffering
- feelings about the circumstances of death.

A literature review (Kaldjian, 2008) reported a list of 6 goals can be used to articulate goal-oriented frameworks to guide decision-making toward the end-of-life and thereby harmonize patients' treatment choices with their values and medical conditions:

1. be cured
2. live longer
3. improve or maintain function/quality of life/ independence
4. be comfortable
5. achieve life goals
6. provide support for family/caregiver.

Discussions about end-of-life care and end-of-life decision-making involve cognitive and particularly affective processes and are often emotionally taxing. How end-of-life discussions are delivered and what is discussed can influence patient's decision-making and affective outcomes.

Although the issue has been increasingly in the public eye, few patients have had these discussions with their physician or family; and, even when they have, decisions may not

be documented in the patient's record. Without plans, a crisis situation can escalate quickly, especially if the patient cannot communicate or if the family's preferences conflict with the clinician's ones. In these cases, treatment decisions are not made, they simply happen, usually based on habits that are presumed to reflect what patients generally want.

ACP can be difficult, there may be actual barriers (Lynn et al, 2007):

- Everyone is reluctant to talk about the patient's declining health and approaching death.
- Clinicians find it easier to offer comfort, hope, and medical technology rather than to "let people die."
- Patients and families find it hard to believe that treatments such as resuscitation will not restore health.
- Clinicians and family may not accept the patient's treatment priorities and values.

Recently the Royal College of Physicians, (2009), has release some Evidence-based Guidelines for clinical management, "Advance Care Planning". In box 3 recommendations are reported about the physician approach to ACP:

- |   |
|---|
| <ul style="list-style-type: none"> <li>• Ideally, ACP discussions should be initiated in primary care</li> <li>• ACP should be offered during routine clinical practice, but never forced upon</li> <li>• Professionals should initiate ACP discussions with patients using their professional judgement to gauge the appropriate time</li> <li>• The professional should have adequate knowledge about the disease, treatment and the particular individual to be able to give the patient all the information needed to express their preferences to make the plan</li> <li>• Individuals should be encouraged to choose who they would wish to be included in the discussion, such as next of kin or future proxy</li> </ul> |
|---|

Box 3. When and with whom should I be considering ACP discussions?

In box 4 the recommendations about the better way to conduct a discussion on ACP with the patients are reported:

- |   |
|---|
| <ul style="list-style-type: none"> <li>• ACP discussions need to be skilfully led and should be a process, not a single event or a tick box exercise</li> <li>• Professionals should ensure that individuals have every opportunity to participate in the discussion by treating reversible illness impacting on decision-making, such as delirium or sensory impairment, and ensuring that the patient is pain-free, fed, not too tired etc</li> <li>• ACP discussions should not be continued if they are causing the patient excessive distress or anxiety</li> <li>• Professionals should take account of the following factors which influence attitudes to discussing ACP, and ensure that these factors do not act as artificial barriers: older people, the professional's own personal experience and beliefs, the patient's gender, race, culture, sexual orientation, religion, beliefs and values, the patient's concerns about euthanasia</li> </ul> |
|---|

Box 4. Recommendations of the RCP on how to conduct a discussion about ACP with a patient.

Finally in box 5 it is clearly reported that all the carers must be trained in ACP discussions and that it is essential to record the patients statements.

- Health and social care staff should be trained in ACP discussions, especially physician, nursing, social workers and other key workers
- Staff training should be workplace-based, recurrent and led by experts and expert patients
- Physicians should be routinely reminded to offer ACP discussion at an appropriate time to their patients
- ACP should be part of the Quality Outcomes Framework
- Medical records should contain a specific section for advance statements
- A register should be created, which stores details about an individual's ACP document, and should be readily accessible with the individual's permission
- ACP documents should be recorded on the electronic patient record (with the patient's consent)

Box 5. Recommendations for training and implementation of ACP

In general, discussion about advance care planning should focus more on goals of care than on specific treatments, and clinicians should be especially careful to respond to the emotional content of the discussion (Tulsky, 2005).

The underlying principle is that the discussion should move back and forth from preferences to reasons and values to information and back, ensuring that the patient understands the implications of his or her stated preferences and that the doctor understands the patients' values. Although little evidence exists to guide practice, it may be more effective for a physician to make a values-based recommendation, rather than offering a variety of choices without guidance (Back, 2008).

## 5. The evidence based practice in palliative care

The palliative approach towards the patient in terminal phase requires that all the health carers are able to provide a high quality assistance.

Palliative Medicine, like any other branch of medicine, needs research to switch from a medicine based on opinions to a medicine based on scientific evidence. Clinicians should make decisions for the individual patient not only under their own experience, but also with the guide of the best available evidence. Evidence Based Medicine (EBM), should guide one's clinical decisions based on the efficacy and safety of a particular intervention in a specific population. But only few patients have average characteristics. In Palliative Care the difficulty with guidance about symptom control often is the paucity of evidence of sufficient quality (Bausewein et al, 2011).

Since the primary studies are rare, clinically heterogeneous, with small sampling and often of poor quality, the scientific evidences in palliative care not always can provide elements of "best practice" in order to lead the clinic practice.

The shortage of the research in palliative care is connected to different concurring factors; among them there are:

- A particular observation/intervention setting: for example the patient residence that makes difficult to realize of complex research protocols;
- The limited survival of the patients, with short observation times;
- Subjective experience of the patient during the advanced phases of the illness, that usually make impossible a preliminary intervention, even more complicated to be realized at the end-of-life;
- The multidisciplinary integration often is problematic;
- Techniques and assessment tools are not always comparable between countries.

Anyway, different types of research protocols can be adapted to the specificity and limitations of the palliative medicine in Primary Care:

- Guidelines Implementation and Clinical audit;
- Descriptive surveys, quantitative researches with valued questionnaires and qualitative researches with unstructured interviews;
- Testing of pharmaceuticals and equipment, specific but not invasive;
- Descriptive studies, with the method of the Follow-back survey, using as source of information the caregivers, etc.

### 5.1 Outcome measurement in palliative care

Outcome measurement has a major role to play in improving the quality, efficiency and availability of palliative care (Bausewein et al, 2011):

- Outcome measurement is a way of measuring changes in a patient's health (which can be attributed to preceding healthcare) over time;
- It can be used to improve the quality of healthcare services;
- Outcome measurement can be used for clinical care, audit and research purposes;
- There is an increasing need for robust outcome measurement in the field of palliative care, but this poses particular challenges and requires special consideration with regard to patients' situations at the end-of-life.

A patient's experience can be related to physical (e.g., symptoms and functional status), psychological (e.g., cognition and emotions), social and cultural (e.g., family and friends, organisational and financial), and spiritual (e.g., beliefs, meaning and religion) domains, which are all interlinked.

Palliative care aims to provide holistic care for patients and families and for this reason an outcome measure should be a complex one and ideally cover several of these domains, as well as aspects of care (NICE, 2011).

Most outcome measures (questionnaire or scales) cover various domains and dimensions, dimensions relate to measurable quantities or particular aspects of a problem: for example, the patient, family and carers, or quality of care, as well as physical (Fig. 1).

A large number of outcome measures have been developed to measure specific physical dimensions, for example, symptoms such as pain, breathlessness or fatigue (Table 3).

Outcome measure	Number of items	Completion time	Notes
Palliative care Outcome Scale (POS)	10 items on physical symptoms emotional, psychological and spiritual needs, provision of information and support	mean time 6.9 min (patients) and 5.7 min (staff)	scores from 0 ('no effect') to 4 ('overwhelming'), staff patient of and carer version; widely used palliative care measure freely available after registration
POS-S Symptom list	10 symptoms 2 questions about the symptom that affected the patient the most and that has improved the most	few minutes	scores from 0 ('no effect') to 4 ('overwhelming'); additional symptom versions available for other conditions (POS-S MS, POS-S renal);
Distress Thermometer	overall distress score 20 symptoms, 5 items on practical problems, 4 on family problems, 5 on emotional problems, 2 on spiritual concerns	median length of time 5 min, with 75% taking no more than 10 min	distress score 0-10; other items yes/no
Edmonton Symptom Assessment Scale (ESAS)	9 symptoms and "other problem"	Approximately 5 min	each symptom with NRS 0-10 developed to measure the most commonly experienced symptoms in cancer patients; freely available
Memorial Symptom Assessment Scale (MSAS)	14 items 7 depression 7 anxiety	2-6 min	developed to assess depression and anxiety for people with physical illness; not freely available
European Organization for Research and Treatment of Cancer - EORTC QLQ-C30	5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea, vomiting and pain), a global health status/QoL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties)	first assessment 12 min (SD 7.5 min), second assessment 11 min (SD 6.5 min)	not freely available, widely used in cancer research; modular supplement available for a range of malignancies (lung, breast, gastric, brain etc.)

Outcome measure	Number of items	Completion time	Notes
EORTC	pain, physical function (3 items), emotional function (2 items), fatigue (2 items), QoL(1 item), symptoms (6 items)	< 20 min	not freely available, shortened, version of the EORTC QLQ-C30 for palliative care patients

Table 3. Examples of multidimensional outcome measures in palliative care (modified from Bausewein et al, 2011)

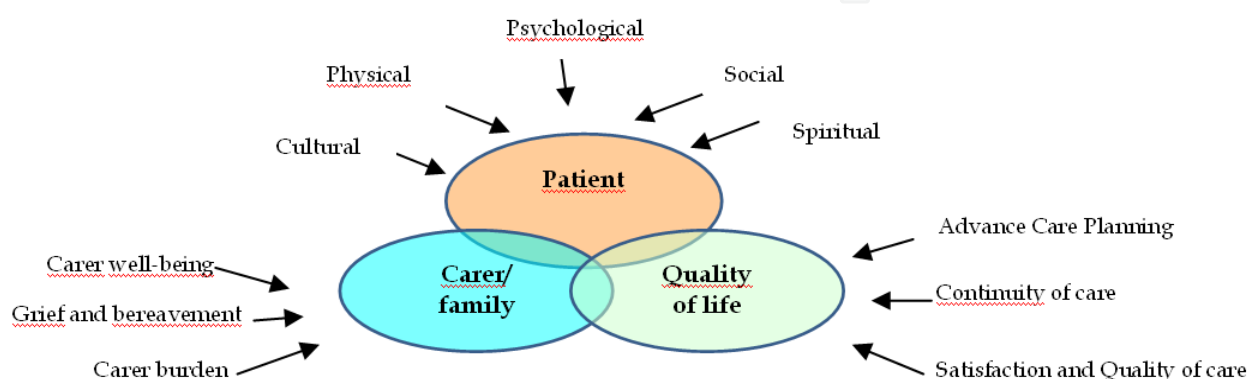


Fig. 1. Domains and dimensions of outcome measures in palliative care (Bausewein et al, 2011)

Psychological symptoms, such as depression or anxiety, are either measured using separate scales or are included in the symptoms’ measures.

### 5.2 Pain therapy in palliative care

Daniel is a 48 y.o. male, suffering from malignant melanoma with liver metastases, abdominal and thoracic lymph nodes and multiple bone metastases (spinal multidistrict). He is receiving 2 cp of 32 mg hydromorphone/day, oral morphine 50 mg every 4-6 hours (rescue dose), bisphosphonates I.V. every 28 days (in hospital), laxative and anti-emetic therapy. For three days there is an intense nausea due to liver metastases. Daniel is no longer able to take oral therapy. His GP would like to change the oral therapy in a parenteral route. What are the available evidences to support the clinical decision making?

Palliative care is operationalized through effective management of pain and other distressing symptoms, while incorporating psychosocial and spiritual care according to patient and family needs, values, beliefs and culture(s).

Pain is a symptom defined as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 1994).



For an adequate estimation of a patient, the Joint Commission Accreditation of healthcare Organization Standard Manual declared in 2002 that the fifth “vital sign” to look for is pain.

Pain has been identified consistently as one of the major problems in end-of-life care.

Chronic pain, present not only in cancer but also in degenerative diseases, neurological disorders, especially in advanced stages and terminal illness, takes on the characteristics of **global pain**, or in other words, of personal suffering, that finds in its etiopathogenesis physical reasons as well as psychological and social causes.

All types of pain (acute, chronic, and cancer pain) are undertreated, and poorly controlled. Adequate pain control can be achieved in most patients at the end-of-life by using a comprehensive approach that includes analgesics, adjuvants, education, support, and monitoring (Emanuel et al, 2011).

Patients should be asked about pain severity, quality, location, and temporal features, such as onset, duration, diurnal variation, or aggravating/relieving factors. They should be actively involved in establishing the goals of palliative pain management, along with family members. It is essential to explain the origin and the type of pain, the initial management plan (including the role of titration), expected adverse effects and how they will be managed, how the pain will be monitored (Emanuel et al, 2011).

### 5.2.1 Pain classification

Pain is a subjective experience, influenced by cultural factors, specific situations and other psychological variables. The process of pain does not begin with the simple stimulation of the receptors. It is influenced by the personality of the patients, the context in which they live, the cultural level and the experiences of life.

As knowledge about pain has advanced, health care professionals have become increasingly aware of the need to develop a more mechanism-based approach to pain control. Cancer pain is a paradigmatic combination of physical and inflammatory processes, that may result from tissue damage and destruction and/or stimulation of nerves by inflammatory mediators produced by the tumor and by the body in response to tumors, too.

Usually pain can be classified as:

- **Nociceptive pain:** is caused by the activation of nociceptive nerve fibers by physical tissue destruction or by chemical, pressure, or thermal processes; often it is described as sharp and stabbing, while the visceral stimulation derived from the receptors present on the internal organs, (such as the bladder, intestine, stomach, etc...), is poorly localized and may be deep or cramping.
- **Neuropathic pain:** A new definition was suggested by the IASP Neuropathic Pain Special Interest Group (NeuPSIG, 2008). This group redefines neuropathic pain as “pain caused as a direct consequence of a lesion or condition that affects the somatosensory system”. Neuropathic pain is difficult to treat, given the variety of etiologies, mechanical causes and symptoms that characterize it, and its impact on different dimensions of health. The pain is of different intensity, that rarely reaches high levels but causes intense suffering to the patients. It occurs as a continuous pain, throbbing or stabbing, with possible hyperalgesia or hypoalgesia, paresthesia, allodynia.

- **Mixed:** both nociceptive and neuropathic pain are common in illnesses like cancer.

There are several methods to observe pain, based on the patient's ability to define it quantitatively. The measurement of pain is a fundamental tool of the assessment and strategy of pain management for pain control. Routinely using the analgesic scales and keeping records of the results in the patients medical card helps improve the ability of the physician to understand the intensity of pain.

Several instruments are used, some complex, others easier to use in the setting of general practice; the two main categories are:

**Intensity scales**, such as:

- **Visual Analogical Scale (VAS)** is designed to present to the respondent a rating scale with minimum constraints. Respondents mark the location on the 0-10 centimeters line corresponding to the amount of pain they experienced. VAS data of this type is recorded as the number of millimeters from the left of the line within the range 0-10 centimeters.
- **Numerical Rating Scale (NRS)** is an instrument that requires the rater to assign the rated object that have numerals assigned to them, instruct the patient to choose a number from 0 to 10 that best describes their current pain, 0 would mean 'No pain' and 10 would mean 'Worst possible pain'.
- **Verbal Rating Scales (VRS)** uses specific words to numeric pain describe rather than a scale. In other words, the person in pain describes the intensity of pain, and how they feel.
- **Analogue Chromatic Continuos Scale** is based on gradation of colour along the line (e.g. pale pink to dark red, for the worst pain)

An objective assessment of physical functioning constitutes an important part of the multidimensional assessment of pain. Terminally ill patients may curtail their physical activity because of pain. Physical activity may also be restricted because of fatigue, cachexia, and drowsiness, common in end-stage illness, contributing to rapid deconditioning, with severe impairments in overall functional status.

**Multidimensional questionnaires** (D'Errico & Valori, 2011) are useful for an overall objective and subjective assessment, but are less used by general practitioners because, if compared with the intensity scales, it means devoting more time to the patients:

- **McGill Pain Questionnaire** can be used to evaluate a person experiencing significant pain, can be used to monitor the pain over time and to determine the effectiveness of any intervention.
- **Memorial Pain Assessment Card:** a scale used to assess 32 physical and psychological symptoms in three different dimensions: intensity, frequency, and distress.
- **Brief Pain Inventory:** provides information on the intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension).

### 5.2.2 Principles of pain control

Pain control is an important aspect of palliative care, in order to improve quality of life. Relief of pain should be seen as part of a comprehensive pattern of care encompassing the

physical, psychological, social, and spiritual aspects of suffering. The various components must be addressed simultaneously. Disease progression may necessitate increased dosing of opioids to control pain; this should not be confused with "tolerance." In fact, when a patient with previously well controlled pain develops the need for increasing opioid doses to achieve comfort, advancing illness is almost always the cause (Emanuel et al, 1999).

Flexibility is the key to managing cancer pain. As patients vary in diagnosis, stage of disease, responses to pain and interventions, and personal preferences, so must pain management. The patient should be actively involved in establishing the goals of palliative pain management, along with family members (ICSI Guideline, 2009; NCI, 2009).

The National Cancer Institute (NCI, 2009) emphasizes the patient involvement in 5 recommendations (ABCDE):

- **Ask** about pain regularly. Assess pain and associated symptoms systematically using brief assessment tools. Assessment should include discussion about common symptoms experienced by cancer patients and how each symptom will be treated;
- **Believe** patient and family reports of pain and what relieves the pain (Caveats include patients with significant psychological/existential distress and patients with cognitive impairment);
- **Choose** pain-control options appropriate for the patient, family, and setting;
- **Deliver** interventions in a timely, logical, coordinated fashion;
- **Empower** patients and their families. Enable patients to control their course as much as possible.

There are many barriers to a good pain management in palliative care (NCI, 2009). They include (table 4) discounting a patient's subjective measure of pain, difficulty in assessment of the cognitively impaired, myths believed by both practitioners and patients about opioid therapy and fears of addiction and hastening death.

#### **Problems related to health care professionals**

Inadequate knowledge of pain management  
 Poor assessment of pain  
 Concern about regulation of controlled substances  
 Fear of patient addiction  
 Concern about side effects of analgesics  
  
 Concern about patients becoming tolerant to analgesics

#### **Problems related to patients**

Reluctance to report pain  
  
 Concern about distracting physicians from treatment of underlying disease  
 Fear that pain means disease is worse  
  
 Reluctance to take pain medications  
 Fear of addiction or of being thought of as an addict. This fear may be more pronounced in minority patients.  
 Worries about unmanageable side effects such as constipation, nausea, or clouding of thought  
 Concern about becoming tolerant to pain medications

Table 4. Barriers to Effective Pain Management (NCI, 2009)

### 5.2.3 Management of pain

The World Health Organization (WHO, 1996) produced a pain ladder to be used as a guide for prescribing analgesics. The severity of pain, assessed by the scales, is classified as mild, (range VAS 1-4), moderate (VAS 5-6) and severe (VAS 7-10) (figure 2). Different type of analgesics are used, depending on the severity of pain. A telephone survey conducted in 2003 in 15 European countries and Israel, which involved 4,839 patients, showed that there is considerable diversity in the use of analgesics in chronic pain. Countries with greater use of NSAIDs were Poland (71%) and Italy (68%). The weak opioids were used by 36-50% of responders in Sweden, UK and Norway, and only 5-9% in Israel, Denmark and Italy. Strong opioids were almost unused in Italy, Spagna and Switzerland (0-2%), while 12-13% were prescribed in the UK and Ireland (Breivik et al, 2006).

In all three steps it also is possible to use an adjuvant therapy (various drugs, chemotherapy, radiotherapy or/and surgery) to strengthen the action of analgesics (figure 2).

Patients who did not improve their pain should go to the next step of the analgesic ladder.

The consensus statement from the American Pain Society and American Academy of Pain Medicine (1996) states that the undertreatment of pain is unjustified.

For many people experiencing cancer pain that is expected to continue, opioids should be administered on an “**around-the-clock**” basis, rather than given only when pain becomes intense. The “around-the-clock” approach provides a consistent level of the medication in the blood, and this helps to provide a fairly consistent level of pain relief, preventing abrupt peaks and valleys of pain, with the use of short-acting opioids as supplemental agents for Breakthrough pain. Controlled-release formulations can lessen the inconvenience associated with “around-the-clock” administration of short-acting opioids.

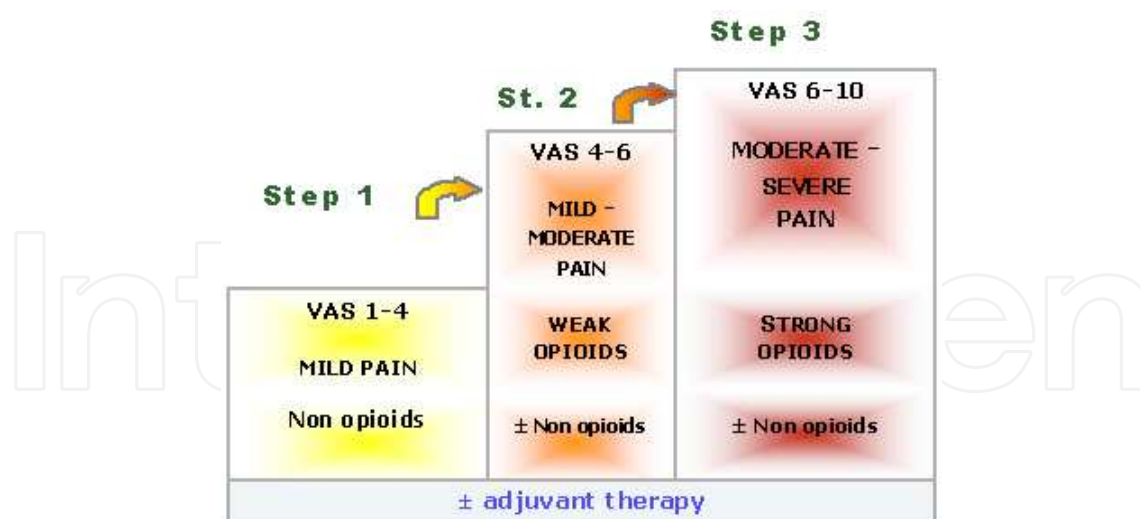


Fig. 2. Pain ladder proposed by WHO (1996).

Recently, the usefulness of step 2 of the WHO ladder has been questioned. Two systematic reviews (McNicol et al, 2004; Maltoni et al, 2005) raised questions about delayed introduction of strong opioids may result in periods of uncontrolled pain. Nowadays, for moderate pain, the recommendation is to consider starting with small doses of a strong opioid. (Pergolizzi et al, 2008).

In table 5, a synopsis of treatment strategies for chronic pain is reported (Emanuel et al, 2011); strong opioids are the reference analgesics for moderate to severe pain both for nociceptive than neuropathic pain.

Type	Nociceptive pain		Neuropathic pain	
	mild	moderate to severe	mild	moderate to severe
<b>Typical Analgesics</b>	Non-opioids ± weak opioids	Strong opioids	Unuseful (?)	Strong opioids
<b>Adjuvant Analgesics</b>	Acetaminophen (paracetamol) or NSAIDs	Acetaminophen or NSAIDs, Radiotherapy, Surgery	Tricyclic antidepressants Typical and atypical anticonvulsants	

Table 5. Analgesic strategies for Chronic Pain (nociceptive or neuropathic).

### 5.2.3.1 Non-opioid typical analgesics

The non-opioid analgesics are both typical or adjuvant analgesics. They include nonsteroidal anti-inflammatory drugs (NSAIDs and COXIBs) and acetaminophen, or paracetamol.

NSAIDs and Paracetamol are recommended for use alone or in combination with opioids both as first line therapy (mild pain) or as adjuvant analgesics (moderate to severe pain).

**NSAIDs** are a group of organic acids with analgesic, antipyretic and anti-inflammatory properties, indicated for rheumatic pain and skeletal muscle inflammation. The effects of NSAIDs are related to inhibition of cyclooxygenase (COX-1 and COX-2) enzyme.

The inhibition of COX-2 determines the analgesic, anti-inflammatory and antipyretic effect typical of **COXIBs**. NSAIDs and COXIBs reduce pain exerting their action primarily at the level of noxious stimuli, which elevate the threshold for activation of nerve endings.

The commonest adverse events with NSAIDs are gastrointestinal (mucosal erosion and bleeding) and renal toxicity.

The analgesic effect of **paracetamol** is expressed at the central level; its mechanism of action is due to inhibition of prostaglandin synthesis in the central nervous system (CNS), but also by the activation of serotonergic pathways descendants. It is administered orally, rectally or intravenously. Oral solutions are absorbed more quickly than traditional tablets and effervescent soluble tablets even better: they contain sodium bicarbonate, the prokinetic action of which promotes gastric emptying and the arrival of the drug in the small intestine that is home to the main absorption.

### 5.2.3.2 Other adjuvant analgesics

**Tricyclic antidepressants** (TCAs) may be useful as adjunctive therapy for cancer-related neuropathic pain syndromes. TCAs provide pain relief by independently providing analgesia specific for neuropathic pain, potentiating the effect of opioids, and improving underlying depression and insomnia.

TCAs (amitriptyline, nortriptyline, and desipramine) are also thought to have an inhibitory effect on nociceptive pain, by raising the levels of serotonin and norepinephrine in the CNS

by slowing the rate of reuptake by nerve cells. Their analgesic activity seems to be independent from their antidepressant effects. Unfortunately, TCAs also block histaminic, cholinergic, and alpha1-adrenergic receptor sites, and this lack of selectivity is what accounts for the unwanted side effects such as weight gain, dry mouth, constipation, drowsiness, and dizziness.

Several **anticonvulsants** (valproic acid, carbamazepine, gabapentin, pregabalin, clonazepam and others) have a role in the treatment of neuropathic pain. They are thought to inhibit seizures by multiple mechanisms, including functional blockade of voltage-gated sodium channels, functional blockade of voltage-gated calcium channels, direct or indirect enhancement of inhibitory GABAergic neurotransmission, and inhibition of glutamatergic neurotransmission. The effects on neuropathic pain, characterized by neuronal hyperexcitability, are probably mediated by the same molecular mechanisms. Their efficacy is quite variable; antidepressants and anticonvulsants may occasionally be prescribed simultaneously, but it is good clinical practice to introduce only one drug at a time.

### 5.2.3.3 Opioid analgesics (weaks and strong)

The most effective analgesics are the opioid analgesics. The opioids include all drugs that interact with opioid receptors in the nervous system. Opioid receptors are a group of G protein-coupled receptors with opioids as ligands. These receptors are the sites of action for the endorphins, compounds that already exist in the body and are chemically related to the opioid drugs that are prescribed for pain. Most opioids undergo biotransformation in the liver and are primarily eliminated by kidneys as a mixture of the parent opioid and their metabolites. Accumulation of active metabolites with analgesic or neurotoxic effects can result in significant toxicity.

WEAK OPIOIDS		
AGONISTS		PARTIAL AGONISTS
Codeine Propoxyphene Hydrocodone Dihydrocodeine Tramadol		Buprenorphine
STRONG OPIOIDS		
AGONISTS		AGONISTS/ANTAGONISTS
Morphine Oxycodone Hydromorphone Methadone Fentanyl Diamorphine	Oxymorphone Meperidine Levorphanol Sufentanil Alfentanil	Pentazocine Butorphanol Nalbuphine

Table 6. Classification of Opioid Analgesics by Receptor Interactions (modified from Emanuel et al, 2011)

Opioid metabolism knowledge helps in initial selection and titrating the dose in terminally ill patients. On the basis of the interactions with the various CNS receptor subtypes ( $\mu$ ,  $\kappa$ , and  $\delta$ ) the opioids can be divided into pure agonists, partial agonists, mixed agonists and antagonists (Table 6). The latter two groups are generally not useful in terminal illness, because of partial or total “ceiling effect” (the effect is not dose-dependent) for analgesia and undesired dysesthesia for the activation of K-receptors associated with some agents.

The EAPC survey in 42 European countries (EAPC survey, 2006) showed that the most frequently used opioid (68%) is morphine (see also table 1). Morphine is referred to as the “gold standard” for pain treatment in palliative care, because it is effective, inexpensive and easy-to-holder. In other countries (18%), such as Italy, Spain, Luxemburg, Austria and Belgium, the most widely used opioid was fentanyl, a strong one, but quite expensive and difficult to titrate. Tramadol, a weak opioid, was the first used in 8% of the other countries.

**Morphine** is the first-choice strong opioid in palliative care, because it is very effective, inexpensive, and easy to titrate. It can administered using many routes including oral, rectal, parenteral, subcutaneous and spinal route. Morphine binds to opioid receptors in the CNS, reducing the perception as well as the emotional response to pain. Alternative opioids have not demonstrated advantages that would make them preferable as first-line drugs for cancer pain. Over the past decade very few new opioids have been developed, but rather new formulations have been made (oral controlled-release formulations, transdermal patches, oral transmucosal devices, buccal adhesive tablets, nasal sprays) to optimise their overall use and to increase usage especially for malignant pain (Janet et al, 2009).

**Oxycodone** is a strong opioid, used to treat moderate to severe pain. The extended-release form of this medication is for “around-the-clock” treatment of pain. In case of insufficient analgesia and/or intense adverse effects such as sedation, hallucinations and nausea and vomiting a switch from another opioid to oxycodone might be beneficial. Oxycodone is mainly used as controlled-release tablets for chronic pain. The immediate-release solution and tablets are used for acute pain or for BTcP. Parenteral oxycodone is a good alternative when opioids cannot be administered orally (Biancofiore, 2006).

**Hydromorphone**, is a semi-synthetic morphine derivative that differs slight from morphine in its chemical structure: this makes it 5–10 times more potent and enhances its distribution into the brain making titration of the effects easier. Hydromorphone may be better tolerated than morphine in patients with renal failure (Felden et al, 2011).

**Fentanyl** is an agonist strong opioid analgesic, effective for the treatment of acute and chronic pain via multiple routes of administration:

- Transdermal fentanyl (Transdermal System – TDS or Patch) releases the opioid for three days, needle-free, easy to use and circumventing barriers to the use of oral analgesics, for example in patients with nausea. The main problem is the dose titration to obtain pain-control: the patch should be introduced only when the pain is under control with an oral opioid.
- Oral transmucosal fentanyl citrate (OTFC), the so-called lollipop, utilizes the rapid uptake through the buccal mucosa to achieve high plasma concentrations rapidly; the OTFC is indicated to treat Break-Through cancer Pain (BTcP).

- The fentanyl buccal tablets (FBT) offer slightly better pharmacokinetics for the same indication, as Fentanyl buccal soluble film (FBSF), a small, bilayered, water-soluble polymer film that adheres to the buccal mucosa and rapidly delivers fentanyl into the systemic circulation.
- The intranasal fentanyl spray (INFS) route is another option to achieve rapid uptake of fentanyl, indicated to treat acute and BTcP relief (Grape et al, 2010).

Despite the current availability of alternatives to morphine, the recommendations of the European Association for Palliative Care (Hanks et al, 2001) on the use of opioids in cancer pain remain still valid. However, most of the recommendations are not based on strong scientific evidence but on the clinical experience of respected authorities from expert committees. Table 7 describes some of the key recommendations.

Grading*	
C	The opioid of first choice for moderate to severe cancer pain is morphine.
C	If patients are unable to take morphine orally the preferred alternative route is subcutaneous There is generally no indication for giving morphine intramuscularly for chronic cancer pain because subcutaneous administration is simpler and less painful.
C	The optimal route of administration of morphine is by mouth. Ideally, two types of formulation are required: normal release (for dose titration) and modified release (for maintenance treatment).
A	Oral transmucosal fentanyl citrate (OTFC) is an effective treatment for 'BTcP' in patients stabilized on regular oral morphine or an alternative step 3 opioid.
A	Hydromorphone or oxycodone, if available in both normal release and modified release formulations for oral administration, are effective alternatives to oral morphine.
B	Transdermal fentanyl is an effective alternative to oral morphine but is best reserved for patients whose opioid requirements are stable.
C	Methadone is an effective alternative, but may be more complicated to use compared with other opioids because of pronounced interindividual differences in its plasma half-life, relative analgesic potency and duration of action.
B	Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered in patients who derive inadequate analgesia or suffer intolerable adverse effects despite the optimal use of systemic opioids and non-opioids.
*The grading system express the robustness of scientific evidence: an A recommendation is sustained by a strong scientific proofs, while a D evidence is mainly based on expert-opinion. Grade B and C express intermediate levels of evidence.	

Table 7. Recommendations about the use of Morphine and alternative opioids in cancer pain (Hanks et al, 2001)

Decision pathway to manage pain in terminally ill patients involves selecting the right opioid at the right dose, frequency, and route, and the prevention and treatment of opioid side effects. Careful opioid titrations with close monitoring of outcomes (eg. pain relief, side effects, physical aid psychosocial functioning) is required to achieve an individualized analgesic response.



- give in adequate dosage
- titrate the dose for each individual patient
- schedule administration according to drug pharmacology
- administer on a strict schedule to prevent pain
- give written instructions for patients on multiple drugs
- give instructions for treatment of Breakthrough pain
- warn of, and give treatment to prevent, adverse effects
- keep the analgesic program as simple as possible
- use the oral route wherever possible
- review and reassess

Box 6. Principles of analgesic administration (modified from Doyle & Woodruff, 2008)

The principles of analgesic administration (particularly for opioid analgesics) in the treatment of chronic pain are summarized in box 6 (Doyle & Woodruff, 2008).

A decision pathway algorithm for opioid therapy (Eti & Heidelbaug, 2011) is reported in Figure 2.

**Opioid rotation**, especially for patients with cancer, should be considered when opioid side effects are difficult to manage. This approach is based on the clinical observation that intraindividual response varies remarkably from opioid to opioid and that a change to an alternative drug may yield a far better balance between analgesia and side effects. The opioid rotation/switching/ substitution is a strategy that includes:

- changing to a different medication by using the same route of administration, or
- maintaining the current medication, but changing the route of administration, or
- changing both the medication and the route of administration,

because of insufficient pain management, intolerable adverse effects, need for change the administration route and economics.

When opioid rotation is applied in the setting of unacceptable adverse effects, the selection of an alternative opioid is largely empiric. A pure opioid agonist is recommended. Opioid rotation has been shown to be useful in opening the therapeutic window and establishing a more advantageous analgesia/toxicity relation (Vadalouca et al, 2008).

Many patients develop adverse effects such as constipation, nausea, vomiting, urinary retention, pruritus and CNS toxicity (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and –rarely– opioid-induced hyperalgesia/allodynia). In some cases a reduction in opioid dose may alleviate refractory side-effects. This may be achieved by using a co-analgesic or an alternative approach such as a nerve block or radiotherapy (adjuvant therapy). Other strategies include the continuous use of antiemetics for nausea, laxatives for constipation, antipsychotics for confusion and delirium and psychostimulants for drowsiness. However, since some of the side-effects may be caused by accumulation of toxic metabolites, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. This is especially true for symptoms of CNS toxicity like opioid-induced hyperalgesia/allodynia and myoclonic jerks (Jost & Roila, 2010).

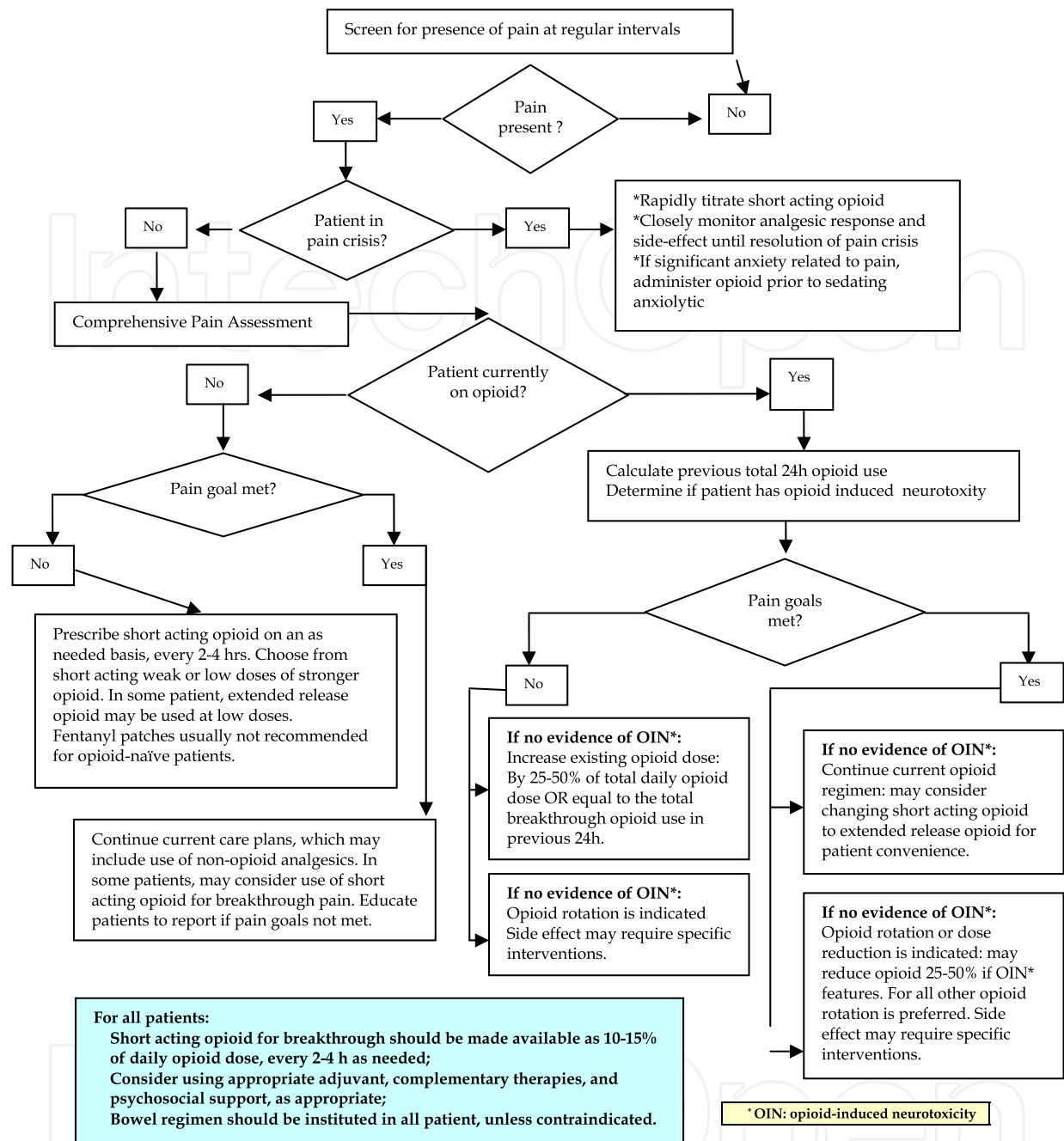


Fig. 3. Pathway algorithm for opioid therapy (from Eti & Heidelbaug, 2011)

Disadvantages of opioid rotation include problems related to inaccurate conversion of the doses, limited availability of certain opioid formulations, drug interactions, and the possibility of increased expense. Weighing the advantages and disadvantages is essential prior to making a decision about opioid rotation selection. This approach requires familiarity with equianalgesic doses of the different opioids (see Table 8).

### 5.2.4 The Breakthrough (cancer) Pain (BTcP)

Breakthrough (cancer) pain (BTcP) is a common problem in patients with cancer, associated with significant morbidity in this group of patients (Davies, 2006). The original definition of

BTcP was “a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy” (Portenoy, 1990).

It appears within a few minutes and lasts about 30-45 minutes, distinctly different from the basic pain, with which it shares the location and irradiation.

A newer version has suggested an extension of the definition of BTcP: “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable

Drug	Oral Route	Parenteral Route	Conversion Ratio to 30mg Oral Morphine (OM)
Morphine sulfate	30mg	10mg	Parenteral morphine is <b>3 times</b> as potent as OM
Oxycodone	20mg	NA	Oral Oxycodone is <b>roughly 1.5 times</b> more potent than OM
Hydrocodone	20mg	NA	Oral hydrocodone is <b>roughly 1.5 times</b> more potent than OM
Hydromorphone	6 mg	1.5 mg	Oral hydromorphone is about <b>5 times</b> as potent as OM Parenteral hydromorphone is <b>20 times</b> as potent as OM
Fentanyl TDS	NA	12-15 mcg/hr TDS	TDS fentanyl is <b>approximately 80 times</b> as potent as OM

Table 8. Opioid Equivalency – Strong Opioid (daily doses)

or unpredictable trigger, despite relatively stable and adequately controlled background pain” (Davies, 2009). The characteristics of pain are:

- High intensity
- Frequent involvement of the same basic site of pain
- Acute clinical manifestation
- Appearance during the day that is repeated with variable frequency

BTcP can place a significant physical, psychological and economic burden on patients. Despite advances in the management of cancer pain, through the application of modern, evidence-based, multimodality management and the availability of new treatment options, recent European surveys have indicated that the diagnosis and treatment of BTcP is still suboptimal. A general lack of consensus on its definition alongside poor recognition and inadequate assessment may often lead to under-treatment and poor patient outcomes (Dickman, 2011).

A task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland (APM, 2009) has produced some up-to-date, evidence-based, practical, clinical guidelines on the management of BTcP in adults. The task group was unable to make recommendations about any individual interventions for the lack of strong evidences; however the group released 12 recommendations about certain generic strategies (Table 9), based on limited evidence (i.e., case series, expert opinion).

Grading*	
D	Patients with pain should be assessed for the presence of BTcP.
D	Patients with BTcP should have this pain specifically assessed.
D	The management of BTcP should be individualized.
D	Consideration should be given to treatment of the underlying cause of the pain.
D	Consideration should be given to avoidance/treatment of the precipitating factors of the pain.
D	Consideration should be given to modification of the background analgesic regimen /“around the clock medication”.
D	<p>Modification of the background analgesic regimen has been shown to be a useful approach in managing BTcP, and may involve one or more of the following treatment strategies:</p> <ul style="list-style-type: none"> <li>• Titration of opioid analgesics. Titrating the opioid can be effective in reducing the intensity and/or frequency of movement-related volitional incident pain (Mercadante et al, 2004). However, his strategy is often limited by the existence/development of dose-dependent adverse effects (e.g., sedation) (Portenoy, 1997).</li> <li>• Switching of opioid analgesics. Switching the opioid and/or the route of administration of the opioid can also be effective in reducing the severity of movement-related volitional incident pain (Kalso et al, 1996; Enting et al, 2002).</li> <li>• Addition of “adjuvant analgesics”. Adjuvant analgesics (“co-analgesics”) are agents whose primary function is not analgesia, but which provide pain relief in certain circumstances (Lussier &amp; Portenoy, 2004). This strategy can be effective in reducing the impact of specific BTcP syndromes (e.g., antiepileptics for neuropathic pain, anti-spasmodics for visceral pain) (Gannon &amp; Davies, 2006).</li> <li>• Addition of other “adjuvant drugs”. Adjuvant drugs are agents whose function is not analgesia, but which provide relief from the adverse effects of analgesic drugs (or the complications of the pain) (Lussier &amp; Portenoy, 2004). This strategy can be effective in allowing titration of the analgesic drugs, which in turn can be effective in reducing the impact of BTcP (e.g., psychostimulants for opioid-related sedation) (Bruera et al, 1992).</li> <li>• Other strategies. In theory, alteration and/or addition of non-opioid analgesic drugs could also lead to improvements in BTcP (e.g., paracetamol, non-steroidal anti-inflammatory drugs) (Gannon &amp; Davies, 2006).</li> </ul>
D	Opioids are the “rescue medication” of choice in the management of BTcP episodes.
B	The dose of opioid “rescue medication” should be determined by individual titration.
D	Non-pharmacological methods may be useful in the management of BTcP episodes.

Grading*	
D	Non-opioid analgesics may be useful in the management of BTcP episodes.
D	Interventional techniques may be useful in the management of BTcP.
D	Patients with BTcP should have this pain specifically re-assessed.
*The grading system express the robustness of scientific evidence: an A recommendation is sustained by a strong scientific proofs, while a D evidence is mainly based on expert-opinion. Grade B and C express intermediate levels of evidence.	

Table 9. Recommendations for the management of BTcP (Davies et al, 2009)

### 5.2.5 Constipation and opioid therapy

Side effects are a common and predictable consequence of the opioid therapy; they may either occur acutely and suddenly or as a consequence of a long-term therapy. The most common side effects are constipation, drowsiness, nausea, pruritus and confusion.

Constipation is one of the most common problems experienced by patients in palliative care, particularly those with advanced cancer. The rate of patients with terminal disease affected by constipation varies from 23% to 87% (Librach, 2010; Noguera, 2009; Larkin, 2008; Lagman, 2005), with the highest incidence observed in patients treated with opioids (prevalence 50-95% in several studies: Clark, 2010; Noguera, 2009; Woolery, 2008; Lagman, 2005). Among opioid-treated cancer patients constipation can cause extreme suffering and discomfort. Despite these data, constipation is often undervalued by all the care providers, since it is considered a minor symptom.

Patients' assesment for constipation symptoms should be done at every office visit and a stimulant-based bowel regimen at the beginning of chronic opioid therapy should be routinely initiate. Recommendations (Larkin, 2008; VaDoD, 2010) for the farmacologic treatment of constipation in palliative care patients are listed below:

- Initial bowel regimens should generally consist of a bowel stimulant and a stool softener as well as general measures, such as increased fluid intake, increased dietary fiber, and adequate exercise.
- If inadequate, mild hyperosmotic, saline, and emollient laxatives may be added.
- If possible, reduce or discontinue other drugs that may cause or contribute to constipation.
- Bulk-producing laxatives, such as psyllium and polycarbophil, are not recommended and are relatively contraindicated as they may exacerbate constipation and lead to intestinal obstruction in patients with poor fluid intake.

A revision of clinical guidelines identified only two documents on the management of opioid-induced constipation in palliative care patients (Woolery M, 2008; Librach S. L, 2010); the recommendations are mainly based on expert-opinions:

- Opioids should not be reduced during the treatment of constipation unless it is absolutely necessary (Librach S. L, 2010);
- Switching opioids such as morphine slow-release oral to transdermal fentanyl may decrease constipation (Woolery M, 2008);
- Replace the opioid methadone can lead to a reduction in the consumption of laxatives (Woolery M, 2008);

- Methylnaltrexone is recommended, as an option, to patients treated with opioids that do not respond to usual laxative therapy (Librach S. L, 2010)

**Methylnaltrexone** (MNTX) is only registered for use in palliative care patients with opioid-induced constipation who did not respond to adequately titrated laxatives, and in whom bowel obstruction has been excluded. MNTX is not a treatment for constipation caused by factors other than opioids. MNTX is an opioid antagonist that, in clinical doses, is unable to cross the blood-brain barrier. Therefore, it can reverse the effect of opioids in the peripheral nervous system and relieve constipation (response of about 50% to laxation after 1 or more doses are given) without reversing the analgesic effect of opioids in CNS (Nerissa & Baumrucker, 2011).

## 6. Conclusions

Palliative care is a holistic, patient-centered, and culturally sensitive approach to care. To have a meaningful effect on patients' quality of life and end-of-life care, palliative care services should be provided earlier in the course of the disease. However palliative care reach the maximum impact if it can establish a good communication and a respectful relationship with both the patient and his/her carers. Giving dignity, space and attention to the communication are essential steps that need to be undertaken by a doctor that recognizes a correct relationship with the patient as one of his main means of cure and essential for a better Advance Care Planning (ACP).

The essence of the doctor-patient relationship makes family physicians ideally suited to provide home end-of-life care. A good primary palliative care is essential, as it allows patients to remain at home as long as they desire. Many patients want to be informed about their diagnosis, prognosis, treatments and related side effects, even though they are "bad news".

Stimulate and record ACP at an appropriate time is a good clinical practice in palliative care. All the carers should receive an adequate training in ACP discussions with terminally-ill patients. ACP statements should be recorded in medical documents and readily accessible to all the care staff .

The role of Evidence Based Medicine (EBM) in palliative care is limited, since the scientific evidences not always can provide elements of "best practice" in order to lead the clinic practice. However EBM can be useful to handle some situations, such as the treatment of pain and other common symptoms in palliative care. Pain has been identified consistently as one of the major problems in end-of-life care. All types of pain (acute, chronic, and cancer pain) are undertreated and poorly controlled. To obtain effective results in the pain treatment the patient should be fully informed on the origin and type of pain and how it will be monitored; the patient should also be involved in the management plan (including the role of opioid titration) and in the treatment of the expected adverse effects (e.g. the constipation).

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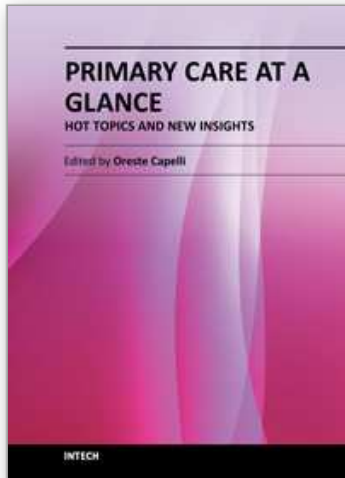
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## **Primary Care at a Glance - Hot Topics and New Insights**

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