Supportive Care in Oncology

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INTRODUCTION

Stating the reason for the preparation of such a complex and all-encompassing book is difficult for a person who is facing the stage of professional maturity. This is yet another effort, perhaps my last one, to provide an updated means of consultation to the doctors of our difficult discipline. I repeat difficult; difficult for its vast horizon that encompasses humanity, intuition, and science, and that unfortunately for years has been practiced as "good" medicine requiring no further refining of knowledge.

The text breathes a very familiar air, based above all on experience first domiciliary and then in hospitals in the field of cancer pain, palliative care, and supportive care, along an evolutionary journey parallel to changes in this discipline. Although the risk is that of self-referentiality, the book really wants to lead the reader along the lines of research being followed in these formidable years, the fruit of a scientific activity persistent in time in the various aspects of this discipline and confirmed by the attention of the scientific and academic world. Those who know these lines of research from following me over the years, know well how these actually reflect a clinical activity with primordial intuitions then confirmed by scientific data published in a wonderful virtuous circle of mutual reinforcement between clinical activity, renewed by research, inspired by clinical activity. The many visitors we have had at La Maddalena Cancer Center in recent years have been able to observe live as the protocols used, the obsession with a deep evaluation, and the need to individualize a treatment to find the most effective solution in the most difficult cases, in other words the life of the department, reflect exactly this plastic paradigm of the need to solve clinical problems, to form new ideas, and perform scientific demonstrations, with a curiosity that is very reminiscent of that phase of maximum mental openness that is typically found in childhood. Here, bringing out the child in us is probably the most daring aspect of this book, flattering the desire for Dante's knowledge, to run through the gardens of science, to admire the details of a painting, to tease their indomitable certainties, to train the movements so as not to accidentally injure yourself, to reassure while infusing doubts.

Palermo, June 2020
Sebastiano Mercadante

PART ONE:

GENERAL ASPECTS OF PALLIATIVE MEDICINE

CHAPTER ONE

PALLIATIVE CARE AND SUPPORTIVE CARE

Palliative care is central to public health for many reasons related to the aging of the population and the development of many degenerative diseases characterized by complex and chronic problems which require specific services and professional solutions. Palliative care is by nature multidisciplinary and requires knowledge of various types that include the physical, psychological, social, and spiritual needs of the patient, interposing in some cases with the etiological treatment of the disease after the point of diagnosis, as in the case of cancer.

Many models have been described for palliative care, often resulting from different national histories and cultures and the availability of public and private economic resources rather than homogeneous long-range planning dictated by incontrovertible epidemiological data (1).

In every country, therefore, palliative care has arisen on the emotional and emergency impulse, with the need, however, to satisfy an urgent need. Consequently, the distribution of services, the available economic resources, the organization, and the quality of care have been quite inhomogeneous across territories.

On the other hand, the observation that patients are living longer due to the improvement of the available therapies is unequivocal. However, the levels of quality of life are low enough for the persistence, moreover now longer lasting, of a symptom burden that requires considerable attention and a continuous care plan. The needs are therefore enormously increased and they sound a warning for organizational and structural reforms.

Yet, already many years ago, the World Health Organization had enunciated the definition of palliative care, through a rigorous examination by pioneering experts who had intuited primordial elements that should have been applied and adapted to changes in the years that followed. Many of these indications have been surprisingly disregarded in many countries, with the introduction of laws, apparently innovative but with unrealistic interpretations of the need for innovation, as a result of ignorance and political obstinacy.

> Palliative care is… applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

In previous years we have witnessed an expansion of palliative care programs, with widespread networks, generally in low-intensity facilities, such as hospices and at home, used to assist sick people mainly in the advanced stages of the disease and in the last weeks of life. In recent years, notable epidemiological and social changes, as well as relevant information from the scientific world, have subverted some traditionally consolidated organizational aspects. The need was therefore felt to further develop this activity beyond the boundaries of traditional structures. In particular, the need for early and simultaneous intervention in causal therapies, which mainly occur in hospitals, has been reimagined. To confirm this, the trajectory of many chronic degenerative diseases and cancer is to show a progressive loss of function with periods of acute crisis along the more or less rapid progress towards death.

Recent studies have affirmed that the use of early supportive therapies allows a clear improvement of the quality of life in terms of the prevention and treatment of physical and psychological symptoms, and in some cases also a prolongation of survival (2). The differences between the traditional pathway of care, with a clear sequential temporal pattern from oncology to palliative care, and the concept of simultaneous care, including early palliative care, are depicted in figures 1 and 2.

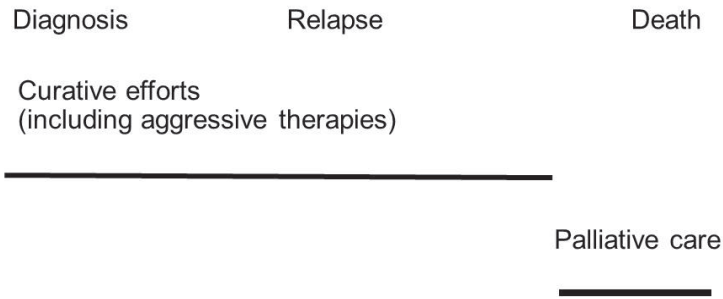

Figure 1. Conventional pathway from oncology to palliative care

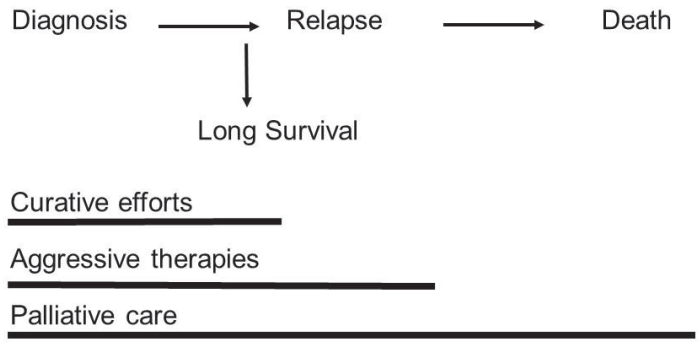

Figure 2. Modern pathway of simultaneous care

Thus, a network of palliative care should include various options with different characteristics, according to patients' needs, which are not interchangeable (table 1).

Care	primary	secondary	tertiary
Personnel	GP, other specialties	PC team	PC team
Setting team	home, hospital	home, hospice	PCU, mobile
Role	basic care	assistance, consultation	assistance, consultation

Table 1. Levels of care (GP = general practitioner, PC = palliative care, PCU = palliative care unit)

It should be more correctly pointed out that while it is understandable that the use of simultaneous supportive therapies can be of benefit during the active treatment of a disease such as cancer, the methodology by which to demonstrate this axiom remains very weak. In fact, in controlled studies to date the definition of "best supportive care" has always been very generic, as has that of the control arms, which obviously does not help us in being able to effectively treat a patient (3). The difference, if proved, continues to be based on the individual treatment of a doctor who follows a patient more or less conscientiously, rather than a well established system of integration.

Thanks to these scientific data, which have shown great advantages for patients, the interception of patients along all the phases of the disease, with the offer of a continuous and gradual service according to the needs, sometimes with more intensive spaces for the resolution of some more complex problems, has modified the traditional and unidirectional vision of palliative care, often recognized as end-of-life care. This underlines the need to provide in hospitals an integrated activity which foresees, alongside the treatment against the disease, the early intervention of a palliative care expert. Also from the terminological point of view there is the need for greater clarity regarding the available treatment modalities.

The complexity of some clinical situations often requires shelter to be provided in a protected environment in order to quickly achieve the control of symptoms, difficult to obtain in other environments (table 2). Consultancy services and units with beds available for high intensity care within a cancer department prefigure an indispensable support for the definition and resolution of the problems of these patients, redirecting the patient, according to a specific evaluation, towards a trajectory of care more suitable and proportionate to their conditions (figure 3). Therefore, in addition to supporting functions, these skills act as a filter and as moderators with respect to the aggressiveness and therapeutic futility observed in recent years. It is disarming to notice that chemotherapy treatments are continued well beyond the most optimistic expectations, with costs often unjustified from both an economic and financial point of view, and from the point of view of damage to the patient, considering that in some cases they cause early death by the toxicity inflicted on patients in precarious physical conditions (4-14). These centers are instead fundamental in the transition to more specific treatments, avoiding the clear-cut transition between so-called active and often disproportionate treatments and end-of-life care, a psychological phenomenon that is fatal for patients and family members, as active care and palliative treatment should be separated by a temporal space.

- Interdisciplinary evaluation and identification of patients' needs
- Treatment of difficult clinical conditions
- Assessment and monitoring
- Oncological re-evaluation
- Constant education for professionals, patients, and relatives
- Bridge with other units facilitating transition to palliative care
- Informal behavior
- High opioid consumption
- Research
- Teaching and education
- Cultural pressure in other units
- Internal and external consultations
- Introduction to palliative care network (hospice, home care)

Table 2. Characteristics of the palliative/supportive care unit at the comprehensive cancer center La Maddalena

The low consumption or the delayed use of opioids, observed in some European countries, is probably linked to these discrepancies, rather than the availability of opioids now widely represented and marketed (15). It is also evident that these centers, having acquired great experience due to the high turnover of patients characterized by considerable criticality, are responsible for carrying out educational, didactic, academic, and research functions for other palliative care services, with an exchange of information and advice, thus allowing continuity of care in the territory (12). This system is also economically sustainable in terms of cost effectiveness, avoiding inappropriate admissions in non-specialist facilities that constitute a cost without providing adequate specialistic performance. In these circumstances, admissions to acute hospitals devoid of palliative care availability are often ineffective and expensive. The resolution of problems of a physical and psychological nature during a short and non-definitive stay during the course of a disease and, once the stabilization of the symptoms has been achieved, the continuation of treatment in a less intensive environment such as a hospice or the home, are an added bonus of services made available in a palliative care network. From this point of view, a specialist clinic is an important strength for the continuous assessment of these patients, who are often lost during the continuation of treatment and who often remain without a reference point (7).

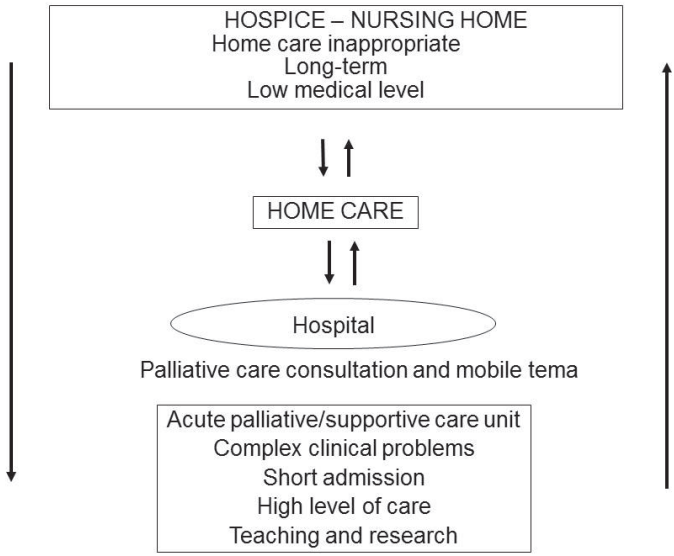

Figure 3.

These perspectives do not replace traditional services, which remain unavoidable, but add another element to a network of services that are not optional but essential for the providing of palliative care (figure 3). Also from the qualitative point of view it is possible to apply some differences in the field of a possible network, according to primary, secondary, and tertiary care, with an expansion of the offer according to intensity levels.

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CHAPTER TWO

BIOETHICS

Bioethics in medicine is a fundamental resource in undertaking difficult decisions in certain contexts. In the field of palliative care, it assumes a peculiar role regarding the social, cultural, philosophical, and spiritual connotations. The burden of physical and psychological suffering, the approach to the end of existence, and the need for difficult decisions in the various stages of an incurable disease, particularly in the last days of life, require the knowledge of bioethical aspects (1). In order not to remain a sterile subject of abstract rules, it is necessary that the principles that regulate bioethics should be considered in a determined clinical context where all information needs to be known. A basic knowledge of different concepts and principles is the common language with which professionals can identify practical solutions. The recourse to the systematization of the ethical analysis of cases in which it is difficult to undertake a decision is fundamental; such decision making must be according to some orderly steps that allow the following of an intelligible path to reach the best possible solution (2).

Analysis

A first consideration concerns the ethical analysis, that is, the identification of the current problem for the formalization of an adequate response. An operational definition of an ethical analysis, albeit within limits, is given by the challenge of resolving a case for which simple clinical and technical information cannot resolve the issue and for which it is necessary to turn to the ethical principles that indicate a solution, often in contrast with the possible technical aspects. A typical example would be: is it acceptable for family members to require of a clinician not to communicate the diagnosis and prognosis to their loved one? Is there an overriding right of the family members or of the patient in this sense? Once the question has been identified, it is necessary to evaluate the principle to be invoked according to the priorities for that individual patient.

Information

Clinical information is essential for the formalizing of an appropriate ethical analysis. A lack of technical information on the diagnosis and prognosis, the therapeutic options, and their risks, benefits, and symptom loading often results in abstract and meaningless bioethical statements.

Individual values and preferences

Exploring the values of life and individual preferences is fundamental in making decisions. Respect for dignity, freedom, and the patient's own thinking, at least in the competent patient, is fundamental. Therefore, the first point is to establish the patient's cognitive and affective level, which requires a professional technical evaluation. In cases where the patient is unable to express these values, a surrogate must be identified. There are profoundly different cultures which envisage conflicting attitudes concerning for example the implicit delegation of decision-making powers to family members, as happens in the Latin world. A lack of knowledge of these details risks severely disrupting the relationship with the patient and family members. On the other hand, in globalized societies, treatment has always been more centered on the patient rather than on the different cultural and traditional values of family members. Therefore, a further effort should be made to differentiate patients according to an individual or parental style, thus respecting their autonomy of thought.

Evaluation of possible alternatives

Beyond the possible therapeutic actions already considered, there are also alternatives on how to pose an ethical question. For example, if the problem concerns the lawfulness of communicating or not the diagnosis to the patient at the request of the family members, we can highlight alternatives to the problem – for example, how to follow the wishes of the family, communicate the truth against the opinion of the family, or review patient preferences.

Formulation of the ethical solution

Having analyzed all the technical and ethical data, one is in the best condition to respond to an ethical question. In making such a decision it is essential not only to explain the reasons that lead to a conclusion, but also to suggest how to facilitate the application of these principles, or to specify

the circumstances of the action to be undertaken according to a typically journalistic scheme (who, how, where, when).

Re-evaluation

Each decision-making experience must be re-evaluated with an accurate reflection on the results obtained in each individual case in which an ethical evaluation of an emerging problem has been expressed. This aspect of concreteness, guided by the value of prudence, makes it possible to direct future actions and acquire greater wisdom.

Traditional principles of bioethics

Benevolence and non-malevolence are traditionally the underlying ethical principles, also called "of reason" – in other words, doing well and avoiding evil. With the evolution of society and culture, the importance of autonomy and justice has been underlined. These four elements represent the typical set of ethical principles that should guide medical decisions. In general, none of these principles has a moral priority over any others (3).

a) Autonomy is defined as the ability to act freely according to one's choices in an unconditional way without interference and limitations. This concept expresses intentionality, understanding of the problem, and lack of external influences. Respect for the autonomy of a patient can be expressed with a negative obligation (for external influences, for example), or positive (respect for individual rights), as long as they do not cause damage to others.
b) Non-malevolence supports the obligation not to determine to cause damage to others. This concept is not always absolute and should be reasonably balanced, since in some cases there are reasons that can justify an intervention that does not intentionally, but may well, lead to a shortening of life, as in the case of the double effect doctrine.
c) Benevolence corresponds to the need to provide a contribution to individual well-being. Positive benevolence compels us to help others, even if this is balanced with utility, or rather the need to balance the benefits and drawbacks, and possibly even costs, of an action. The use of *quality-adjusted life years* is a typical example of the application of the utility principle.
d) Various theories of justice have been proposed, based on concepts of equality and health costs. It could be defined as the right to use health

services in the context of available resources and incorporates utility and equality – in other words, a distributive justice.

Personalistic bioethics

The principles of bioethics have also been dealt with according to different views. Personalist bioethics involves the defense of life and death, the therapeutic principle, freedom and responsibility, and sociality and subsidiarity – points based on concepts of phenomenological philosophy that rest on an anthropological basis. Respect for human life and dignity are the fundamental moral values of our society and a precondition of the common good (3).

The first point provides that life, not necessarily the state of health, is an indispensable asset and an ethical imperative. On the other hand, it supports the dignity of death as a fundamental value that justifies, for example, interventions that involuntarily can accelerate death (double effect doctrine). In fact, experiences in terms of terminal sedation have made it possible to exclude the possibility of an anticipated death, using specific protocols and adequate monitoring and above all with highly professional management, even if there is a risk, observed in some countries, of deliberately accelerating the death, in prevalently unprepared environments, albeit in a context of imminent death (see chapter 26). On the other hand, the same doctrine of double effect, accepted by the Catholic world, could be misleading because it would allow us to glimpse the doubt that sedation can actually accelerate death,

- The therapeutic principle of totality specifies the conditions by which a medical intervention must be legitimized from the ethical point of view. It is more specific than the bland concept of benevolence. The intervention must:

a) protect the life and well-being of the patient
b) be directed to the cause of the disease
c) have no alternatives
d) be expected to be better than or equal to the risk
e) be carried out with informed consent.

This principle therefore affirms the moral obligation to use the therapeutic means available to preserve life or restore health. In this case it does not solve the dilemma of a patient who refuses an intervention despite the potential benefits or who accepts high-risk interventions. The limit of moral obligations to ensure health is evident. The principle of therapeutic proportionality makes a distinction in this sense, adding a non-irrelevant

element (4). It is argued that there is an obligation to offer the best possible treatments that ensure a reasonable hope of preserving life or restoring a state of health or otherwise that there is no obligation for interventions that do not offer reasonable possibilities. This principle makes a distinction between ordinary intervention, in which traditional treatments are used, and extraordinary intervention (5). Therefore, in order to verify whether a given intervention is compulsory, it is necessary to judge the usefulness of an intervention in a specific circumstance. The concept of utility and futility must therefore be placed in a dynamic context rather than circumscribed at the time, and the final judgment cannot be the result of a simple cost-benefit equation (6).

- The proportionality of an intervention depends on the individual clinical situation and therefore the decision does not concern the individual medical intervention but rather the general context. The need to assess the weight of an intervention in its wider meaning is clear and includes the physical, psychological, spiritual, family, social, cultural, and financial aspects of the context. Therefore, once again a professional knowledge of the most technical aspects is fundamental for a moral judgment on the obligation of an intervention. From the clinical point of view the necessary elements are constituted by the certainty of a diagnosis, the relationship between the utility and futility of the intervention under discussion, the risks and the adverse effects of the possible alternatives, and the accuracy of the prognosis. The moral relevance of the concept of proportionality is based on the possibility of distinguishing between the moral obligation of an intervention, the possible options, and the illicit intervention. The lack of observation of this principle corresponds to a malpractice, such as the omission of a lawful intervention or, on the contrary extreme, an intervention that is disproportionate to the circumstances. Many good or seemingly charitable treatments actually result in an aggressiveness or futility of intervention and would therefore be worthy of bioethical evaluation (7).
- Respect for dignity is a fundamental ethical principle in the personalistic conception. This concept is expressed by respect for human life and by the principle of freedom and responsibility. It is therefore presumed that a subject is able to operate freely, but according to a rational scheme, that is, to realize a responsible exercise of his freedom. A violation of this right corresponds to an act of malevolence. With respect to the concept of autonomy already mentioned, the positive dimension of freedom is

emphasized rather than the negative one, i.e., the capacity for self-determination towards one's own good, and therefore concerning one's own structure, rather than the mere possibility of choice without illegitimate obligations, and therefore an external condition. The connection between freedom and responsibility is underlined. For a free and self-determined decision it is necessary to know the appropriate information. Therefore, the communication of a truth, for example a diagnosis, is not simply the opposite of a lie, but a manifestation of mutual respect (8). Deception, on the other hand, is contrary to this principle, since it contravenes the right to know the truth. In palliative medicine, the problem of communicating the diagnosis or the nefarious prognosis is certainly one of the most complex. The reluctance to share clinical data is often associated with family pressures, particularly in Mediterranean countries, according to a culture that predicts that knowledge of the truth can be detrimental to the patient's psychology, increasing anxiety and depression. It has been observed instead that the sharing of truth can have initial negative effects but limited in time, while with limited information the psychological effects persist for a long time due to the isolation and silence that prevent the sharing of one's own fears, anxiety, and other personal problems (9).

- The principle of sociality and subsidiarity describes the value of an individual as part of a community and therefore the obligation to contribute to the common good and to provide assistance to others, especially the most fragile. The dying patient is an example of vulnerability and requires the respect and competence to preserve his life (or his death) and dignity (10).

These different modes of thought are often complementary and not necessarily incompatible. All lead back to a common thread, or to the habit of using these arguments in making a difficult decision in a specific case encountered in the clinic, although there are many commonalities between the personalistic approach and the philosophy of palliative care: the affirmation of life and respect for death as a natural process, without accelerating or delaying its event. The dying person has the right to receive competent assistance by the addressing of the different components of global suffering with compassion and unconditional respect for life and dignity. In clinical practice three elements are therefore needed: clinical competence, compassion, and respect for human dignity, especially in conditions of extreme vulnerability. These elements are

closely connected. The term compassion is often confused with pity. Rather, it should be considered the ability to understand and share the suffering of others, and at the same time the desire, and therefore the better ability, to alleviate it.

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CHAPTER THREE

COMMUNICATION

Communication is one of the most important aspects in palliative care for patients with a progressive disease such as cancer because of the fear and uncertainty that add a strong emotional element in the interaction with clinicians. It reflects the ability to exchange ideas, information, and thoughts. This process can be considered as a form of the application of ethical principles in relation to the exchange of information with the patient, especially in some topical conditions, such as diagnosis, prognosis, continuation of treatment, suspension, transition of care, artificial nutrition, the approach to death, and the need for sedation. Communication, which should be carried out continuously to improve its effectiveness, is often limited to the essential, often as solely a formal and legal fulfillment, rather than being empathically oriented to the well-being of the patient and the family. In medical practice, apart from experience and good individual attitudes, there are mandatory steps to communicating effectively (1).

a) Information

It is essential to acquire information on the reasons for a consultation. In addition to knowing the clinical conditions in detail, it is necessary to know how patients have previously learned about the disease, any problems in the relationship between the patient and family members, and what has been reported in relation to a consultation with a palliative care doctor. Therefore, it is advisable to contact the referring physician for an update on these aspects.

b) Environment

A fundamental requirement is the creation of an atmosphere in which the patient is at ease and feels to be considered as a person, compared to any previous paths that have not been always positive. A good doctor-patient relationship that includes trust, respect, empathy, and complicity is the main requirement for good communication. The use of the gaze, contact, and position, for example sitting at the patient's bed, showing

interest and respect, are non-verbal expressions that can help in the beginning of a relationship. Often the expression of a good mood and a smile, which is not exaggerated or out of place, is a good way to continue the interview because it inspires trust and dispels the commonplace notion of the gloomy and circumspect doctor.

c) Identification

The explicit presentation of oneself as a palliative care physician, even if apparently it could evoke the fear of death and the loss of hope, has instead a overriding characteristic: to start the building of a relationship, avoiding misunderstandings. An explanation of the intent, not necessarily the end of life care, can favor this approach. It is necessary to emphasize that the interview does not represent a therapeutic abandonment and to introduce the elements that can be positive for the patient, such as continuity of care and therapeutic collaboration not conditional upon the clinical conditions , multidisciplinarity, and attention to specific aspects. Aspects related to the need to introduce a palliative care consultation early when the patient continues active care fit precisely in this sense, because these aspects favor a smooth and painless transition.

d) Facilitation

Before communicating any information, it is necessary to elicit the patient's problems, to induce him to speak, to listen to the perceptions and reactions in everyday life. This will allow the patient to relax and be more forthcoming. Some patients may be reluctant to open up or be particularly pessimistic about opportunities for improvement. In these cases it will be necessary to encourage him by trying to solicit the emerging problems that concern him. The patient should not be interrupted, but rather encouraged to continue if a break is granted. Finally, it will be important to show that you understand the problems of the patient by summarizing a set scale of priorities for any problems that have emerged. It is important not to close the interview without setting a new appointment, showing availability at the new meeting.

e) Empathy

Expressions of empathy regarding the emotions shown by the patient and the family allow a reduction of the levels of anxiety, through our asking, for example, his opinion on the arguments discussed so far. This will allow the patient to feel at the center of our attention and understand that his opinion is important. Respect moments of silence (2).

Normalize a strong expression
Understand what kind of emotion
Give a name to the emotion
Make non-verbal gestures of understanding
Encourage to keep talking
Make synthesis and reformulation of emotion
Foment an appreciation of the manner in which care was taken
Embrace silence

Table 1. Strategies for coping with emotions during a consultation

Discussion regarding the diagnosis and prognosis with the patient and the family is a topical moment and is crucial in the planning of decisions, objectives, and priorities, and eventually in preparing for the end of life, if one thinks it is the right time, respecting the feeling of the patient (3). From an ethical point of view, it means respecting the principle of autonomy and self-determination. Moreover, communication is a pillar of informed consent. Most patients want to know all the information possible by which to cooperate and it is the doctor's duty to answer the questions and problems posed about the clinical conditions, the prognosis, and the treatment options. There are good reasons to inform the patient, as good information provides a better collaboration in future choices, creates less anxiety, and also engenders a certain complicity and confidence. Nevertheless, there are often doubts over completeness. In some cases the doctors, for example, feel that they do not have to underline the toxicity of a new treatment because of the fear that the patient will be terrified, and generally try to maintain an optimistic attitude.

However, in some cases it is legitimate to profess optimism for some patients, generally of low cultural profile especially in some geographical cultures, as patients may not understand well or delegate family members. On the other hand, the same principle of autonomy states that the patient may have the right not to know (4). In different cultures, therefore, personal autonomy has different meanings. The doctor should prepare to identify the level at which the patient or family members wish to be informed about the situation and possible options, to face the emotional impact and help to make the right decision. Knowing the previous level of information a patient holds, and even more understanding what the patient would like to know, are essential before starting such a topic. While in the Anglo-Saxon and North-European world patients prefer to be duly informed about diagnosis, prognosis, and therapeutic options, in Latin-Mediterranean culture patients do not want such complete information,

with a clear conflict between the need to know and the fear of learning the truth or of the confirmation of a suspicion held in balance by hope. In many cases, the family is delegated to acquire information, especially in the less developed social levels and in the elderly.

Patients with a good level of culture and young people tend to request complete information. Some patients wish to have less information with the progression of the disease, and psychologically prefer to distance this type of discussion, while family members require more information, perhaps even on the expected survival (5). Even if prognostic factors have been identified (see chapter 4), it is advisable not to be precise when defining exact times that could be disregarded, except in cases where a verticalization of clinical conditions is sufficiently evident. However, it is not always possible to reason on the basis of geographical, social or epidemiological data, and therefore it is necessary to clarify for that given family group what are the attitudes and preferences regarding important information according to the individual characteristics. Advance directives (living will) represent the process by which patients, informed about some basic clinical data, articulate their future preferences (6). This implies an extreme determination and autonomy of the patient, which is not always observable in many cultures. In the United States, these directives are particularly promoted. This is confirmed by legal procedures to which physicians and family members can refer, when the patient will no longer be able to decide and family members take legal responsability for their loved one. This moment can be an occasion for reflection for the patient due to the numerous problems at the end of life. The reinsurance that has been planned to take place automatically is generally favorable and improves trust in the care team (7). On the other hand, many conflicts between family members, emerging in chaotic hours full of emotion, can be prevented. Some doctors are reluctant to start a discussion of this type, due to a lack of time, stress in dealing with patients and family, and the fear that the patient will interpret it as a sense of abandonment. In some cases, advance directives do not provide for the exact course of events and new needs remain uncovered from the point of view of the indications. In others, the necessary documents are unavailable at the culminating moment.

There are some rules in discussing end-of-life decisions with the patient or family (8):

a) Ensure that the patient or family members are ready to discuss these matters. While the pro-activity of the doctor is indisputable, it is useful to understand whether one is ready to do the same or wants to postpone the moment. As mentioned, some patients prefer

to delegate family members. The effectiveness of the discussion seems to be better when all the actors are present.

b) Know the patient's values and priorities, expectations, and concerns.
c) Structure the discussion on end-of-life care goals and patient wishes and concerns.
d) In the Anglo-Saxon countries the discussion of some end-of-life options (non-resuscitation order) is very frequent. In this case it is necessary to offer one's own opinion, avoiding, however, inappropriate counter-questions such as asking "what would you do in case of cardiac arrest", harbingers of an inappropriate emotional load. If the patient comes to a decision, assure him that everything possible will be done to satisfy his wishes.

The discussion should take place early, progressively, and across several sessions to dilute the emotional load, although generally these issues are not appropriately addressed with the right timing. The palliative care physician is often demanded or otherwise forced to deal with these sensitive issues. Therefore the acquisition of the empathic skills needed in this field requires considerable experience and continuous and inevitable exercise in coping with difficult situations. Avoiding these responsibilities is a source of serious professional distress, which results in burn-out (9).

Patients may be furious, even if not visibly. The facial grimace, the tone and the volume of the voice, and gesticulations can testify to a strong emotion that requires listening and help. The patient may insist on the same topic with increasing intensity. Such frustration requires he be given the help that he feels has been denied. A fearful attitude and an unsolicited attempt to justify the ineffectiveness of one's intervention or, on the contrary, a reaction of anger, are avoidable errors. Understanding anger and mitigating it is the first step to a subsequent moment of reasonableness in which the patient will be able to express the causes of his anger. In the re-articulation of the question on which one is insisting it is a delicate matter to make the patient perceive that we understand the problem and their hopes and that we are not disengaging from solving the problem. However, a trap to avoid is getting stuck in trying to support the patient in a simplistic way, arousing new hope and becoming enclosed in a dead end without solution. Concretely, it should be explained that all possible help will be provided in a realistic way, in successive steps that will be explained. In some cases the anxiety is such that it dominates the discussion. In these cases, once again, the re-articulation of the request is the most appropriate response, acknowledging the serious concerns that

are generating their anxiety. To declare that there are no guarantees of success can appear to be very defensive and shift the focus to a treatment's limits rather than to the patient's hopes (2).

The expectations of family members often conflict with reality. The disbelief of the family in the face of the inevitability of the clinical situation is another problem to be modulated. This should be done realistically, exposing the current situation and that which is imminent, going over the clinical history and the treatments carried out,. On the other hand, it is possible to shift attention to new needs, such as for example the limitation of suffering. It is important to underline how distress is greater when expectations are far from reality, and therefore these communication efforts also concern the well-being of the family members. It can be helpful to obtain an eventual confirmation from the doctor who had been treating the patient previously, on completion of the therapeutic procedure, and on the inappropriateness of further treatment lines due to the potential for greater suffering and even for a shorter survival time because of the accumulated toxicity with previous treatment lines. Of course, this also applies to surgical procedures no longer indicated for the current circumstances. Family members will show understanding of the words, but will probably not remain convinced, and will probably insist further. Continuous meetings with the whole family entourage and the elucidation of the clinical events that confirm the above allow the achievement of a full awareness of the reality on the part of the family members.

Some relatives may still not be satisfied with the explanations and will ask for highly toxic or unproven efficacy treatments and will show considerable distress as they do not accept reality. Responding to such family suffering with further treatment is a serious mistake. Listening to and sharing the discussion about alternative treatments and quietly offering one's own opinion may be helpful to the circumstance. Doctors do not have the task of correcting hope, which is the construct of their future. The problem arises when this conflicts with future planning. The physician's task will therefore be to provide an empathetic support presence in line with realistic goals.

On these occasions, it is necessary to maintain considerable self-control by trying to judge when the patient who is facing an issue is having problems in controlling his emotions. It is advisable to induce the patient to talk about his own story, to offer his own co-responsibility for anger, and to show the desire to help him to solve the problem. This inevitable emotional burden must not affect the personal life of the doctor. The use of already tested paths, the experience in and continuity of this exercise, and above all the habit of not avoiding this responsibility will allow a

progressive adaptation to the facing of strong emotions expressed by patients or by family members.

In some cases, the patient or family members may be aggressive and belligerent. Emotions spring up quickly, are volatile, and persist for a long time. In these cases, rather than talking about emotions, which would only contribute to increasing the emotional burden of the moment, we need to divert our attention to behaviors, move the plane from empathy to containment, for example inviting the patient to sit down, drink, breathe, and eventually resume the discussion a few minutes later, a sort of re-enactment. We must expect the belligerent attitude to surface again. Threatening to suspend the session is a serious mistake and represents a bad professional performance.

On the contrary, there are situations in which patients appear absolutely calm and show that they understand the indications provided. Later we realize that the patient is not adherent and cooperative in meeting those conditions that seemed to be shared. This means that despite the apparently good compliance, the interaction with the doctors has not worked, often for cultural reasons or beliefs that determine a vision of the world very far from reality (10).

There are other clinical situations in which a conflict may emerge, even in the more properly palliative atmosphere, such as with the use of antibiotics, hydration, or parenteral nutrition. Antibiotics will be administered with a symptomatic objective, but their use should be balanced against the use of injection systems, costs, and distress for the patient. Therefore, the decision must be individualized according to a realistic expectation of response and proportionality of care in a given context. The problem of nutrition has a very important symbolic meaning and requires a flexibility based on skills and the right indications (see chapters 2 and 24b). The need for artificial nutrition is often a source of disagreement with family members, even in the last days of life. A consultation with family members should direct information on the ineffectiveness of food in certain circumstances. An intelligible explanation must be provided that nutrition at some point loses its clinical significance, presenting as an elementary but comprehensible exemplification (... the patient is not dying due to fasting, but it is the disease that prevents him from using the nutrients ...). A rather controversial topic concerns hydration. A good level of hydration is important in treating many symptoms, but it is deleterious and futile in the last hours of life, particularly when the process of dying has begun and the patient is deeply unconscious or sedated (see chapter 26).

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CHAPTER FOUR

PROGNOSTICATION

In the last months or days of life, patients can make important decisions about their personal or health issues, if they are aware of their life expectancy. For example, they can plan all pending business or not accept medical treatment (1,2). Also, from a medical point of view the prognosis is fundamental in making decisions in relation to risks and benefits. In the advanced stages of disease the risks clearly prevail over the benefits. In fact, a treatment can have different outcomes if it is carried out in different phases. In a patient with poor performance and limited chances of survival, a chemotherapy course, which could be effective in reducing symptoms and controlling the disease a few months earlier, produces dangerous complications in the last weeks of life (3,4).

Similarly, a palliative surgery, an invasive procedure, or the use of parenteral nutrition, which could be indicated a few months earlier, loses its meaning if applied during the last weeks of life. In addition, an accurate prediction of survival can allow the patient to look for palliative care advice. Palliative care services are generally based on a 6-month cut-off (3), although this limit can be questionable. Therefore, clinical decisions depend on the survival predictive capacity in relation to the state of the disease and the patient's clinical condition. The prognosis is formulated subjectively thanks to intuition, knowledge, and personal or objective clinical experience, and therefore in a more reproducible way, through the use of some prognostic tools.

Subjective prognosis

Despite the availability of validated tools, the prognosis is often based on subjective clinical predictions, which are generally more heterogeneous, more variable, and substantially more optimistic than reality (4). The survival prognosis should not be considered as a definitive event, but as a process that varies over time on the basis of the response to treatment, the development of complications, or the worsening of pre-existing diseases. Therefore, the prognosis must be reassessed over time

whenever major problems occur. For example, at the time of diagnosis, when illness recurs, or in any case of a new hospitalization, the evaluation of the prognosis should be re-discussed. In fact, the prognostic factors vary depending on the stage of the disease. While at an early stage the biological characteristics of the tumor condition the prognosis, in the advanced phase, a heterogeneous term generally associated with a survival of a few months or weeks (5), the factors relating to the patient, their physical condition, and some symptoms, such as cachexia, dyspnea, and delirium, prevail in setting a prognosis (6).

In this context, the accuracy of the prognosis is random, not only because it is not always reported in the literature, but also because of the different methods used for population type and time intervals. The discriminative capacity of these tools makes it possible to distinguish how many patients have died or not in a given period of time. It is not always possible to predict survival with certainty (100% sensitivity and specificity), simply because death is just a probabilistic event. For example, with the progression of the disease, more and more disastrous and unpredictable events can occur. Therefore, a therapeutic decision will be taken only with an approximation of months and weeks.

Clinical prognosis

Prognosis can be set differently. For example, a common numerical question is “how long will this patient have to live”. The answer will be linked to a numerical estimate (one week, 6 months, etc). While the question is simple to formulate, the answer is more difficult to understand (is it a mean, a maximum, or a minimum expectation?). The communication of an end-of-life date is still always inconvenient from the psychological point of view. The temporal predictions of physicians are generally more flattering and depend on the experience of those who formulate them, even in the advanced stages of illness (4.7, 8). For younger patients, predictions are always less accurate.

A second way of asking the question is related to unexpected death within a certain period of time. That is, “would you be surprised if the patient were to die in a specific time frame?” In this case the answer is binomial (yes or no), and not linked to an approximate number. However, doctors may have a very individual and variable “surprise” threshold in relation to the established time frame (one week, six months, one year). Finally, the question can be probabilistic, that is, concerning the probabilities of survival in a determined period of time. An accurate answer requires a probability of at least 70%, because less striking answers

push towards uncertainty (for example 60 vs 40%). This has the advantage of not giving misinterpretations of the term surprise. This method is closer to the reality of the temporal approach (4), but paradoxically it loses its effectiveness in the last phases of life. Estimates of nursing staff seem to be closer to reality. All these data confirm that the accuracy of a prognosis depends on the time at which a prognosis is formulated, on the staff, and on the method used, which is substantially subjective.

Prognostic factors

To better target a prognosis, factors related to the disease or the patient have been used. The reduction of performance status, dysphagia and anorexia-cachexia, delirium and dyspnea (4) are the best known clinical factors associated with short survival. The first two conditions are an expression of a progressive deterioration due to the disease with a high inflammatory response responsible for loss of appetite and weight. Delirium and dyspnea, although potentially reversible, are commonly seen in the last days of life, when they become irreversible. Other measures have been taken into account as prognostic survival factors, such as markers of cellular integrity and hydration (phase angle) or muscle strength, and maximum expiratory pressure.

Some biochemical alterations have shown a predictive value: increased C-reactive protein, a marker of inflammatory reaction, leucocytosis, lymphopenia, hypoalbuminemia (index of malnutrition), hypogonadism (associated with loss of muscle strength), hypercalcaemia, and hyponatraemia (9).

Prognostic models have been developed using some of the factors analyzed. The most validated are proposed in table 1. In these models the total score is calculated by the number and weight of the prognostic factors and the probability of survival in a given period of time. Despite the plethora of prognostic models, it is not clear which is the most accurate.

Model	Variables	Score	Interpretation
Palliative prognostic Score	Clinical prediction (0-8.5) Karnofsky 10-20 (2.5) Anorexia (1.5) Dyspnea (1) Leucocytosis (0-1.5) Lymphopenia (0-2.5)	0-17.5	0-5.5 = months 5.6-11 = weeks 11.1-17.5 = days
Palliative prognostic index	Performance scale (0-4) Delirium (4) Dyspnea at rest (3.5) Introduced nutrients (0-2.5) Edema (1)	0-15	0-4 = months 4.1-6 = weeks 6.1-15 = days
Glasgow prognostic score	Albumine < 35g/l (1) C-reactive protein > 10 mg/l (1)	0-2	0 = months-year 1 = months 2 = weeks

Table 1: Prognostic models

Another aspect concerns imminent death. There are simple and reproducible clinical signs that seem to provide unequivocal data for an imminent death (10). Reduction of blood pressure, increased heart rate, very low Karnofsky value, anorexia, dyspnoea, and cyanosis are strongly associated with death within one week (11). The aspect of communication of prognosis, a very important element due to the wide psychological and ethical repercussions, is discussed in chapter 3.

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CHAPTER FIVE

QUALITY OF LIFE

Improving quality of life (QoL) is one of the main goals of palliative care. The meaning of this concept, however, is somewhat imprecise from the social, psychological, and more strictly medical point of view. It could be defined generically as something that concerns what is important in one's life, or more specifically as oriented towards one's own health with particular regard to symptoms and one's capacity, or by the way in which a disease can modify the psychophysical condition. It is evident that this concept is completely individual and linked to the subjective perception of satisfaction, happiness, and well-being. Some literature has focused on the concept of normality, while other studies have addressed mental capacities, such as that of decision-making autonomy, the physical, psychological, and spiritual well-being of one's own family, and relationships with others. The synthesis can be the minimum need to feel that we live adequately: the biological, relational, or occupational need or the need for changes in one's life; in other words, having the level of psychophysical ability for relationships with others, and a mood comparable to what is believed to be happiness (1).

Not always are normality and biological function able to express the level of QoL, as shown by severely disabled patients who express a good level of QoL. For this reason, QoL has been defined as dependent on the relationship between individual expectations and the perception of a given current condition (2). Paradoxically, the two variables can change simultaneously to the same degree and not give rise to any variation in the QoL.

In palliative medicine, QoL is strongly considered a multidimensional concept that concerns symptom control, physical and social function, and psychological well-being, as well as existential and spiritual aspects. From the historical point of view, the WHO in the eighties suggested that health should be considered not only as the absence of disease, but also the state of physical, mental, and social well-being (3), key elements that constitute the three-dimensional axis with which QoL is evaluated. Karnofsky status, initially used to evaluate the physical repercussions of a chemotherapy regimen, has made a strong contribution to research as a treatment-

sensitive evaluation tool, expressed with an easily reproducible scale, which expresses the functional state and at the same time provides a prognostic tool (4,5) (table 1). Indications that are probably obsolete in certain contexts are also provided, such as the need for hospitalization, which is now often rendered unnecessary by the availability of adequate home care.

Definition	Value %	Condition
Able to perform normal activity. Does not require special care	100	Normality, no disorders related to illness
	90	Normality, minor signs
	80	Normality, signs of illness
Inability to work, home life, autonomy with the need for care	70	Unable to perform active work, Ability to self-heal
	60	Requires occasional assistance, but self-sufficient for the most part
	50	Requires assistance and medical care
Inability of autonomy, requires treatment, progression of the disease	40	Disability, requires special assistance
	30	Strongly disabled, need for hospitalization
	20	Very serious, hospitalization necessary for active treatment
	10	Dying
	0	Death

Table 1. Karnofsky performance status

In the subsequent years various instruments have been developed by different oncological groups, with similar linear scales consisting of various domains, such as general well-being, mood, anxiety, pain, and physical and social activity (LASAs), similar to what is reported with the multidimensional pain scales. Other tools are focused on the perception of one's own health (Sickness Impact Profile, Nottingham health profile, SF-36), and yet others on the psychological aspects (General Health Questionnaire, Profile of Mood States) (1). It is evident that the intentions, perspectives, and contents are different and may not necessarily provide equivalent and homogeneous results for the entire population considered. Most of the QoL measurement tools are based on standard questionnaires that are self-compiled by patients, whose main limitation is the lack of knowledge of which interval is more correct to use over time. Another concept, more recently introduced, is that of the results reported by the patient (Patient-reported outcome), that is, a spontaneous report compiled by the patient without the interposition of questionnaires or explanations. In this way, the patient is free to focus on the most important aspects of health for himself, even if any standard of scientific repeatability is lost.

General aspects

In recent years, many evaluation tools have been proposed. Often different words have a similar meaning both regarding the indicators and the areas to be explored. From the point of view of palliative medicine, the most relevant dimensions are represented by the symptoms, and the physical, emotional, and spiritual function reported by the patient, the family members, or the evaluators under certain conditions. The QoL in this context is the perception of the patient's state of health, directly reported by the patient without intermediation. It is a dynamic phenomenon with different explorable dimensions to be selected according to individual factors such as symptoms, illness, cooperation skills, and phase of disease. The content concerns the severity of physical symptoms, general health, spirituality, and existential problems. However, very debilitated patients often cannot complete a questionnaire and the measurement can only be done indirectly using approximations of the case.

As mentioned, different populations can provide conflicting data. Therefore the evaluation methodology requires specificities. Indicators may be used to describe a population, such as survival, type of treatment, or weight of symptoms. For example, patients receiving chemotherapy have elevated Karnofsky levels (> 50) and an expectation generally greater than six months depending on the aggressiveness of the tumor. Some

patients are receiving a palliative care treatment with a survival of a few months, and others have a very low Karnofsky (<40) with a prognosis of weeks. In turn, such patients may present cognitive disorders or not. Therefore the content and the length of the QoL measuring instruments, and the use of indirect observers will have to be considered preliminarily in the choice of a questionnaire. It is foreseeable that the number of missing data will be progressively higher as we observe patients with decreasing survival. In these phases, patients can be helped to complete the questionnaires or it will be necessary to take recourse to family members. The risk here is an overestimation by family members of the patient's psychological distress, which, however, diminishes the concordance between patient and family evaluations.

Assessments by the family members seem to be more accurate when the questions are more concrete and understandable. Some simple and short tools, such as the Edmonton Symptom Assessment Scale (ESAS), are able to provide reliable data with compilation by family members (6). QoL scales are multidimensional in principle and often present interpretative problems. For example, though a reduction by a certain amount in the intensity of a symptom may correspond to the same variation in another symptom or item measured in terms of disturbance to the patient, the sensitive limits to the degree of variation perceptible by the patient may be different. The final result, in the context of predictable psychophysical deterioration, is difficult to appreciate. Finally, it is to be noted how, inevitably, the perceptions of normality, of well-being, and of the interactions with a variable such as the disease and its burden of psychophysical symptoms are difficult to measure because of the completely different individual responses from patient to patient, beyond the clinical course.

Specific tools for assessing QoL

Generally, the choice of a multidimensional tool is recommended. The choice depends strongly on the objective set by the researcher or the evaluator. The tools are generic and/or disease specific, such as EORTC-QLQ-C30 and FACT-G, or area-specific, such as fatigue, pain, or psychological distress, developed for specific groups of patients. In some cases, generic or disease-related tools are combined with more specific areas (pain), for example the effectiveness of a treatment in a given clinical condition and the possible benefits on pain or dyspnea. The number of questions should be sufficient to provide useful information and at the same time not be too heavy for the patient. So if the questionnaire

for an area does not offer particular benefits on a generic or specific tool for the disease, it will result only in a further burden for the patient. Some tools, developed for a certain type of population, for example patients with non-cancer pain, often become translated into palliative care, but are not always similarly calibrated for different populations. It is quite evident how the various instruments follow different constructs (some focus on the symptoms, others on more generic aspects, and others on existential areas). Individual interpretation can be highly variable and the possibility of a change in response over time must be considered (7). For convenience, among the hundreds that exist, only the most common questionnaires and their indications will be examined.

a) General tools

The Short-form 36 (SF-36) is a second-generation tool developed from a more substantial previous one, with a short-term and a long-term version. It consists of 8 domains, for a total of 36 issues: physical, psychological, independence, social, environmental, spiritual relations, and global QoL. The World Health Organization Quality of Life (WHOQOL) covers six main domains: physical, psychological, independence, social relationships, spirituality, and environment for a total of 100 questions. For this reason a shortened scale has been proposed with 26 questions.

b) Specific tools for sickness

The EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer) consists of 30 questions to explore the physical, cognitive, emotional, social, and symptomatic domains. It has been tested in numerous cancer diagnoses, and is repeatable every week. A shorter questionnaire has been used for palliative patients (8). The Functional Assessment of Cancer, general version (FACT-G), provides 27 questions that explore physical, social-familial, emotional and functional well-being, and is repeatable every week

c) Specific tools for areas

The tools described above may not be sensitive to some specific problems, such as pain, fatigue, or psychological symptoms. They are described in the appropriate chapters concerning pain, fatigue, sleep, and delirium.

Specific tools in palliative care

a) The McGill Quality of Life Questionnaire (MQOL) is one of the most widely used tools in advanced patients. In this questionnaire the existential need is strongly considered, which is predominant with respect to the weight of the symptoms.
b) The Therapy-impact questionnaire (TIC) provides 36 questions that assess the impact of disease and therapy and is divided into four domains: physical symptoms, functional status, emotional and cognitive aspects, and social interaction.
c) The Missoula-VITAS quality of life index includes 25 questions for 5 domains: symptoms, function, interpersonal relationships, well-being, and spirituality, and focuses mainly on the most advanced phase for care planning and decision making.

In the advanced stages of the disease, cognitive impairment makes evaluation difficult, even if mediated by family members. Thus attention should be placed on the family members themselves and their perception of QoL and on the existential and spiritual aspects. In this phase, therefore, the previous questionnaires are difficult to apply.

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CHAPTER SIX

SPIRITUALITY

Religious and spiritual aspects are of considerable interest in the relationship between patients, family members, and the palliative care team (1), even if the specific value in terms of the benefit for patients remains ambiguous, particularly because spirituality in principle must be considered a completely individual concept (2, 3).

Personal life is full of unexpected and critical events that go beyond the individual's responsibilities, for example in the presence of important diseases such as cancer. This sort of unpredictable event is associated with symbolic implications of death, and induces an intense emotional reaction of fear, anger, and depression that is typical when faced with a loss of control and independence. Religious belief and language are in fact part of one's own being, even if in this age the role of religion seems to have faded. When a patient faces a critical phase of life, he is instinctively confronted on this ground in search of support.

Spirituality is a broader concept of religiosity, which includes faith and inner peace (4). The mind is continuously nourished by the perception of the meaning of life and has an innate capacity to develop a propensity for spirituality to provide a universal existential response. The spirit is therefore the life force that animates our existence and, like any psychological phenomenon, is intangible (5). Human beings are motivated to identify the meaning of existence in a way that goes beyond their individuality. Spirituality is therefore a very general term that includes different dimensions or expressions, from the concept of the soul to anthropological and cultural developments up to faith and the rituals connected to it.

The connection with the transcendental aspects of life is perhaps the most important aspect of spirituality and manifests itself according to the culture and faith of the individual, in turn belonging to a field of culture, country, family, or group that will have influenced his own psychic structure (1). These connotations are the foundation of the identity of each person. For some, the transcendental connection is represented by a superior being, while for others it is represented by natural events (5).

Religiousness is a fairly complex phenomenon that influences the lives of human beings and the meaning of many aspects of everyday life, such as the sense of happiness and the response to traumatic events (6). There are some elements of religion that can usefully help patients control stress reactions (7). The variation in the development of spirituality is quite wide, from an absolute disinterest in spirituality to absolute faith as the principle that determines life (8). The development of spirituality depends on an individual's maturation, the period of life they are in, and those events that can shift one's sense of life in one way or another. The central aspects of spirituality include the meaning of life, the value of "standard" beliefs, transcendence, relationships with oneself, with others, with higher beings, and with the environment, and the sense of belonging.

Spiritual assistance

In general, the religious are considered the main spiritual assistants in a palliative care setting. One of the main differences between the activity usually carried out in a church and that in a hospital is that in the second case the assistance is offered to a subject belonging to different religious expressions, so the care should be based on the values of the patient. This aspect requires a cultural effort and specific experience which also takes into account the many multi-professional skills that work on an advanced cancer patient. The different forms of spirituality and culture in different countries require different approaches. In addition to their professional skills each member of a team develops their own spiritual dimension (1). Professionals, oncologists, and palliative care experts should know the most common spiritual methodologies and the spiritual history of their patients (8).

Each member of a team should acquire the basic knowledge to approach the spiritual problems expressed by patients. There are multidimensional tools that allow us to evaluate these aspects (9). The SPIRIT scale evaluates spiritual beliefs, personal spirituality, integration with a spiritual community, and ritual practices and restrictions, with implications for clinical management and the planning of the terminal phase. The Systems of Belief Inventory is a tool that measures quality of life and individual responses to the disease, religious and spiritual beliefs, and social support from the community that shares the same beliefs.

- Discover the sources of strength and support for the patient
- Enter into your spiritual dimension
- Explore the thought of God or the meaning of prayer
- Share thoughts with doctors and nurses
- Share the silence

Table 1. Suggestions for the spiritual assistant

The creation of dedicated spaces where patients and spiritual assistants can discuss these problems facilitates communication between the interlocutors (10). In addition to supporting patients and their families, the chaplain can support the team by suggesting the most important steps to be taken, and may work on those members who are continuously exposed to a stressful environment due to patients who face intense suffering daily (11).

Spirituality is a subjective experience related to the individual sense of connection with something transcendental and which manifests itself in a complex interaction of emotions. The appreciation of the positive aspects of these emotions is the key to obtaining psychological benefits in the context of palliative care (12). The ability to appreciate the present moment is the main point to work on. The valorization of time is fundamental, even in a patient with serious physical suffering (13). A second aspect concerns the past, the reconstruction of positive elements, the meaning of one's own existence, and one's own importance. A third scheme concerns the recognition of spirituality in one's life and reconciliation with the controversial points of one's own existence. The search for spirituality translates into some questions: who am I, how do I show my need for compassion, how can I share my uncertainties and hopes, and how do I find the right prayers for myself?

Do not avoid the patient's emotions and feelings
Do not worry about the patient's spiritual requests
Do not offer simple and verbal prescriptions
Do not use metaphorical language
Provide honest answers, addressing their uncertainties and doubts

Table 2. Suggestions for doctors and nurses

Spiritual aspects, unlike psychological problems, cannot be reduced to guilt or unresolved conflicts in the past but are, rather, an expression of the basic needs to reconnect with others or find meaning in one's life. Variations are observed not when the personal crisis appears, but when

spiritual needs are satisfied by sharing one's thoughts with others, by prayer, meditation, or by encountering a community of faith. Reformulating one's psychosocial concerns and needs such as spiritual problems can foster the overall process of the existential improvement of the patient and can stimulate doctors and nurses to consider and use psychosocial interventions with more integrated and extensive spiritual profiles (29, 30).

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Part Two:

Pain

CHAPTER SEVEN

NEUROPHYSIOPATHOLOGY OF CANCER PAIN

In recent years, knowledge of the pathophysiology of pain has made considerable progress, allowing a better evaluation of the elements that underlie its transformation from a warning signal, limited by duration, to the presence of a noxa, to a real disease in itself due to the perseverance of anomalous mechanisms that correspond to the plasticity of the nervous system, that is, that correspond to the ability to adapt to persistent tissue or nerve damage or to the administration of drugs. In the case of cancer pain, these phenomena are even more complex due to the involvement of numerous factors that interfere with the evolution and responsiveness to opioid analgesics.

Nociceptors and afferent nerve fibers

Afferent neurons carry information from damaged peripheral tissues after receiving stimuli from nonspecific structures that act as nociceptors, sensitive to mechanical, thermal, and chemical stimuli. Almost all the myelinated wide A and β fibers normally conduct non-harmful stimuli. The nociceptors Aδ and C are activated by stimuli of different intensities through the homonymous fibers. Such fibers have a small caliber and are non-myelinated, and are more specialized. Their function is to convert various kinds of stimuli into electrochemical signals activating the central nervous system (1). When the stimulus intensity increases, high threshold receptors, normally silent, are activated. The substance P, which activates a cascade of events including the release of nitric oxide, a potent vasodilator, the degranulation of mast cells with further dilatation and extravasation of histamine, and the release of bradykinin, is released in the primary afferents following stimuli of a different nature. These are powerful algogenic substances that sensitize the receptors favoring the release of prostaglandin E2 and cytokines.

Due to these chemical reactions, the adjacent nociceptors sensitize themselves, with an increase in the spontaneous activity of the terminal nociceptors and a lowering of their discharge threshold (2). The state of increased sensitization to peripheral stimuli is defined as peripheral

hyperalgesia. The release of these mediators is therefore able to reduce the activation threshold with an increase in the response to a given stimulus: inactive receptors are unmasked and recruited to amplify these stimuli, in some cases plastically modifying their state. A series of mediators amplifies these processes. The nerve growth factor (NGF) is an important modulator of the nociceptive function and is responsible for the development, maintenance, and regeneration of peripheral nerves (3).

The substance P also activates the neurokinin-1 receptors, which are expressed in the spinal cord. Neurokinin-1 is transported along the sympathetic and sensitive fibers in a retrograde manner, thus contributing to an expansion of the original receptive fields. This phenomenon corresponds to a central hyperalgesia, due to prolonged and intense spinal cord stimulation (see below). Immune cells sensitize or further activate the primary afferent neurons producing acidosis, particularly by neoplastic cells, and favoring the expression of further receptors. These alterations can also induce a response of the autonomic nervous system, which reacts with an increase in its sympathetic efferent fibers (sprouting) around the dorsal ganglia (4).

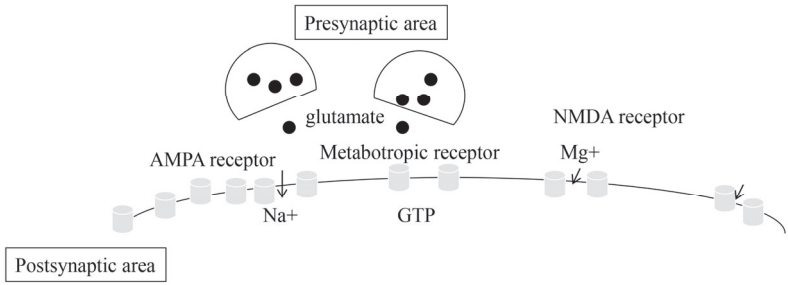

Figure 1. Synaptic transmission in normal conditions. The released glutamate binds to AMPA receptors with consequent opening of the sodium channels and depolarization. The metabotropic receptors bind GTP to G-proteins and activate a second messenger (PKC). The opening of the Mg+ channels blocks the flow of Ca ++ through the ion channels

Spinal cord activation

The pathophysiology of afferent neurons in the dorsal horn of the medulla is particularly complex. Most transmitters are concentrated in the gelatinous substance. The peptides involved are the substance P, the

"calcitonin gene-related peptide", somatostatin, and galantine, as well as glutamate and aspartate.

There are three main receptors for glutamate at the spinal level: AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid), the metrabotrophics, and NMDA (N-methyl-D-aspartate). Peripheral inflammation produces a persistent discharge which induces a continuous release of synaptic mediators. NMDA receptors are silent in basal conditions. Their activation requires the release of glutamate, the binding to its receptor, the presence of glycine, and the means to remove the physiological levels of magnesium ions that normally block the canal. The central sensitization is consequent to the activation of the NMDA receptors that induces and maintains the spinal events and a net state of excitatory hyperactivity. NMDA antagonists, such as ketamine, can reduce excessive spinal response to NMDA nociceptive stimuli, improving analgesia, with an effect that can be defined as more anti-hyperalgesic than analgesic. Antagonists of other neurotransmitters are not well characterized, but have interesting potential for exploration (5).

The central sensitization follows the peripheral sensitization. There are two types of neurons in the dorsal horn that respond to nociceptive stimulation: the specific nociceptive neurons and the high-spectrum neurons, called wide dynamic response (WDR) neurons, which respond to a wide range of stimuli, have extensive reception fields, and increase the discharge proportionally to the intensity of the stimulus. Both NMDA and tachinin receptors are involved in central sensitization. Normally, the activity of the Aδ and C fibers induces a response from the WDR neurons through the release of glutamate, substance P, and neurokinin A, with a slow potential of about 20 seconds. The long duration of these potentials causes a summation during the arrival of numerous low frequency stimuli, generating a progressive depolarization of long intensity and duration in the dorsal horn neurons.

This cumulative depolarization leads to a further activation of neurotransmitters. The ion channels bound to the NMDA receptor, physiologically blocked by magnesium ions, are open to this intense cellular depolarization which leads to a passage of calcium and sodium ions, able to further promote depolarization (6).

Tachinins bind to their receptors through the activation of a triphosphate protein induced by glutamate and produce the depolarization and activation of second messengers, through protein kinases. Thus, a series of postsynaptic mechanisms leads to a state of neuronal hyperexcitability. Modifications of the second messenger can modify gene expression, thus producing a self-extending alteration over time. Intense

peripheral stimulation leads to the rapid expression of the c-fos mRNA gene in the dorsal horn. Therefore, the activation of NMDA receptors causes an increase in intracellular calcium concentration, an upregulation of nitric oxide, and the production of c-fos. The last named encodes a protein (Fos) that controls the expression of other genes (neuropeptide Y, calcitonin gene-related peptide, substance P, and neurokinin A). The activation of Fos is considered a cellular marker of an over-excitatory event (6). Therefore, following prolonged and intense tissue or nerve lesion, there is an increase in spinal neuronal excitability that is responsible for an expansion of the reception fields, an increase in the amplitude and duration of the response to important stimuli, and a reduction of the discharge threshold (7).

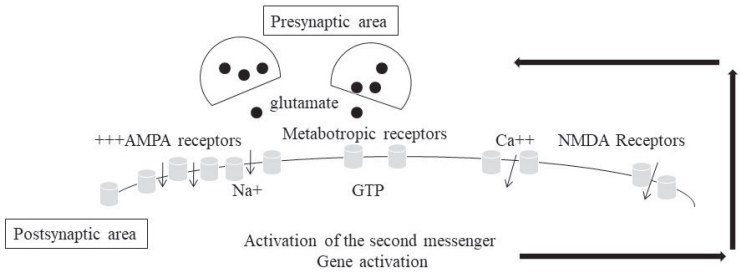

Figure 2. An intense and prolonged stimulus causes a greater release of glutamate. A greater quantity of AMPA receptors are activated, inhibiting the M + blockade on NMDA receptors. Ca ++ ions cross the ion channels interacting with the second messenger, which genetically induces further production of AMPAL receptors.T he phosphorylation of the ion channels makes the cell more excitable. Retrograde messengers also act on presynaptic terminals, releasing further glutamate

Ascending transmission pathways

The nociceptive information is transmitted through the spinal root ganglion to the superior structures through axons ascending along the anterolateral quadrant of the spinal cord. The spino-thalamic tract projects to the ventro-posterolateral nucleus, involved in the discriminative aspects of pain. The motivational and affective aspects are probably transmitted through the projection via the spino-thalamic tract to the medial area of the

thalamus, and to the spino-reticular and spino-mesencephalic areas. The thalamus plays a key role in both experimental and clinical pain. Stimulation of the thalamic nucleus produces antinociception. The role of the cortex appears less defined. The somatosensory cortex contains specific nociceptive neurons projecting from the ventro-posterolateral area of the thalamus. On the other hand, stimulation of the cortex produces pain. Imaging studies have shown that the cortex participates in the nociceptive process, in particular the somatosensory part and the somatic-sensory secondary cortex, the anterior insula, and the anterior cingulate gyrus.

Descending pathways of modulation

The descending system is the most important mechanism for the modulation of nociceptive transmission at the spinal level. The major descending path for pain modulation originates from the periaqueductal area and the locus ceruleus, and extends to the nucleus of the raphe magnum and to the dorsal horn of the medulla through the longitudinal dorsal fascicle to terminate at laminae I, II, and IV of the medulla. A biphasic modulation by the descending system has been postulated, through facilitation and inhibition processes following the activation of cells named for their function: "*on-off*". In the presence of a peripheral stimulus that activates the spinal cord, the descending system implements a counterbalance through the opioidergic pathways, activating the *off cells* and decreasing the discharge of the *on cells*, which instead facilitate the nociception (8). The meaning of the facilitating network is less known and becomes active in certain circumstances. For example, the chronic administration of opioids induces neuronal plastic changes at the level of the periaqueductal substance with an increased production of cholecystokinin. This substance activates the facilitating system with a descending medullary projection. At the spinal level, dynorphine, a substance able to evoke the release of excitatory transmitters from the primary afferent fibers, is overexpressed. This circuit is called into question in the development of opioid tolerance for a reduced inhibitory activity and therefore a reduced antinociceptive effect. The descending antinociceptive noradrenergic system contributes equally to the modulation of the painful stimulus. The α-2 adrenergic receptors, especially the α-2a subtype, have been identified in the gelatinous substance of the medullary dorsal horn. Pre- and post-synaptic actions have been demonstrated. The stimulation of α-2 adrenergic receptors inhibits both the release of activated neurons from A-δ and C fibers and

the release of substance P into the dorsal horn. The antinociceptive effects of α-2 adrenergic drugs are partly due to the release of acetylcholine at the spinal level. Serotonin has a relevant function along the descending pathways and is the target for most antidepressant drugs, although its effects are complicated in different neuronal states (9).

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CHAPTER EIGHT

PAIN MECHANISMS

Cancer pain may initially be a signal of a lesion that leads to the diagnosis of cancer or the recurrence of the disease or may be caused by diagnostic-therapeutic procedures. In some cases the elimination of the cause, for example after an oncological treatment, can reduce its intensity, but in many other situations, during the evolution of the disease the cause persists or reoccurs. At this point the pain loses its biological function and takes on the status of a chronic disease characterized by frequent changes in mood, sleep, and behavior.

It is estimated that cancer pain has a relevant prevalence, with higher percentages (80%) in the advanced phase of the disease. Cancer pain is mainly due to tumor invasion of somatic, visceral, or nervous structures (70%). However, an increasing number of patients present painful pathologies due to antineoplastic therapies (25%), while in a lower proportion of patients, about 5%, pain is attributable to pre-existing comorbidity (1).

There are several painful conditions with operating mechanisms influenced by the characteristics of the tumor and its evolution, the preferential sites of metastases, and the type of treatment performed. Pain related to neoplastic disease is traditionally classified as nociceptive (somatic-visceral) and neuropathic. The term nociceptive is applied when the pain is commensurate with the tissue damage associated with a lesion, well identifiable at the somatic and visceral level. It is presumed that the persistence of pain is related to an existing stimulus that induces the activation of nerve structures responsible for the transport of peripheral, thermal, tactile, and chemical sensations, which take on painful features for certain stimulus intensities. The nociceptive pain that originates from somatic structures, superficial and deep tissues, such as the skin, the subcutaneous tissue, the joints, the muscles, the serous membranes, and the periosteum, is well localized and described as cutting or pressing. From the clinical point of view, these forms seem to respond effectively to opioids or interventional techniques. Anti-inflammatory drugs are also quite effective, due to their prevalent peripheral action mechanism. In

some cases it is possible to exploit the peripheral effect of opioids (in mucosal or cutaneous lesions). In neuropathic pain, on the other hand, there is a strong involvement of the nervous structures, with an aberrant production of stimuli, and a sensation of pain disproportionate to the extent of the lesion. This type of pain is often poorly tolerated and difficult to control. In clinical reality these forms coexist in their various components and it is not always possible to distinguish an isolated mechanism.

Visceral pain

Visceral pain originates from primitive or metastatic lesions of the viscera and abdominal and pelvic organs. The incidence is high (around 45%) (2). The viscera present a quite complex and not completely clear innervation. Differently from their somatic counterpart, visceral nociceptors do not have a warning function, but have a wide range of responses due to different inflammatory stimuli, due to distortion or distension of the hollow viscera. Therefore, they can be considered polymodal nociceptors. The neurons that transmit the visceral sensory information to the spinal cord present their body in the dorsal ganglia and have their terminations directly in the viscera. These afferents have strict relationships with the sympathetic and parasympathetic pathways. Most visceral afferent pathways are of slow conduction velocity (3).

a) Pathophysiology

Two distinct sensory receptors have been proposed for the innervation of the abdominal organs and viscera: high threshold receptors, generally mechanical, activated by stimuli of certain intensity, and low threshold receptors activated by stimuli of lower intensity. High-threshold receptors contribute to the coding of painful events. Prolonged or intense stimuli, such as hypoxia or the inflammation of tissues, would lead to the sensitization of normally silent and inactive receptors that are not responsive to harmless stimuli. The activity of the afferent fibers and bone marrow excitability increase with intense and persistent stimuli following the release of chemical substances into the damaged tissues. Furthermore, the normal profile of motor activity and secretory activity is also altered by local damage produced by inflammation, producing a series of environmental modifications of nerve endings.

Visceral pain tends to be widespread due to the lack of a separate visceral transmission pathway and a lesser representation of visceral

afferents than somatic fibers. The characteristics of visceral pain are shown in table 1.

a) Not evoked by all viscera. Most of the viscera and solid organs are numb.
b) Independent of typical painful stimuli, such as the section for example.
c) Widespread, poorly located and reported in other locations
d) Associated with motor and vegetative reflexes

Table 1. Features of visceral pain

Some spinal neurons are able to locate the stimulus and are projected centrally, while another group of neurons has a shorter ascending projection that sends numerous collaterals at the level of the spinal segments. The activation of spinal efferents could induce alterations of the excitability of multiple spinal units, including those responsible for somatic nociceptive pathways, or a direct activation of neurons that receive both somatic and visceral stimulation. Furthermore, the brain can misinterpret the activities produced at the level of visceral neurons. Convergent receptive fields are generally described as multidermatomic, centered on the dermatoma corresponding to the stimulated spinal segment, and are much more extended than the receptive fields of spinal neurons that receive only somatic stimulations. These observations explain why visceral pain is harder to localize and is often referred to other areas of the body. The pain that originates from a viscus cannot be easily differentiated from that which originates in another viscera, even if the description of some clinical forms takes on quite recognizable peculiarities.

Mechanical stimuli such as torsion or traction of the mesentery, distension of a hollow organ, distension of a mucosal surface, or the compression of some organs produce pain. These situations are frequently observed in patients with abdominal disease or intraperitoneal masses (4). When the intraluminal pressure of a hollow organ increases above a certain threshold, pain appears. Obstruction or inflammation within the biliary or pancreatic tract induces pain due to an increase in intraluminal pressure and the consequent release of inflammatory neuromodulators. The capsular distension of the liver due to an increase in volume produces pain. The distension or traction of the gallbladder produces a deep epigastric pain, especially with deep breathing, associated with nausea and vomiting. A spontaneous spasm of the sphincter of Oddi or that induced

by the administration of morphine produces an increase in the painful sensation, also called paradoxical pain. On the other hand, opioids counterbalance this effect by increasing the threshold necessary to produce this sensation. Renal colic can be traced back to a ureteral obstruction and consequent distension of the upstream tract. This situation is more evident in the presence of abdominal masses that compress or invade the ureters, as in the case of gynecological pelvic tumors. The pain can also appear for direct compression of the bladder or rectum.

The etiology of pain from visceral tissues may also result from ischemia, particularly in damaged tissues or after surgical procedures. The variability of ischemia response depends on the pre-existing pathology or on the mechanical distortion of the viscera due to neoplastic growth.

Chemical stimuli and inflammatory substances released by the tumor can produce irritation of the serous membrane or mucosa. These mechanisms seem to act mainly as co-stimulants, since sharp lesions, such as cutting, do not produce important responses from the experimental point of view, as they more frequently occur with stretching or distension. Improved stimulus localization appears when the disease extends to somatic structures such as the parietal peritoneum. Therefore, initially visceral pain is poorly localized due to the wide divergence of visceral afferents at the spinal level. The best identification of location occurs when somatic structures, such as the peritoneum, are involved in the disease. Somatic structures can also be involved indirectly. For example, diaphragmatic irritation due to abdominal distension produced by large sub-diaphragmatic masses may induce shoulder pain associated with hiccups.

b) Clinical implications in cancer pain

For the previously described qualities, visceral pain appears quite late and should be considered a deep pain apart. It is often referred to somatic structures and can exhibit a status of cutaneous and profound hyperalgesia. An example of reported pain may be low back pain in the presence of pancreatic cancer, or shoulder pain in liver cancer.

Visceral pain patterns are useful in explaining the results of some neurolytic techniques used for the control of abdominal pain. The ineffectiveness or partial success of these techniques can be attributed to the fact that the tumor has spread beyond the nerves that lead pain through the sympathetic plexuses (celiac and hypogastric). Somatic pain is caused by the involvement of the peritoneum, the diaphragm, or retroperitoneal or vertebral structures. Furthermore, quite varied conditions – such as neuropathic radiculopathy pain due to diffusion to retroperitoneal

structures, mucosal pain from chemotherapy, chemoembolization, postoperative or post-radiotherapy – can be associated. These phenomena appear quite late in pancreatic cancer compared to other abdominal diseases. The concomitant pain of somatic origin cannot be found in the neurolytic block of sympathetic plexuses and requires other complementary pharmacological measures. These problems are even more relevant for lower abdominal pain, since pelvic tumors tend to extend much earlier to the muscular and nervous structures present in the pelvic floor, often damaged by previous treatments such as surgery or radiotherapy (5) (see chapter 20) .

Most analgesics are effective for this type of pain. Anti-inflammatories (see chapter 12) and opioids determine a dose-dependent inhibition of visceral responses to distention (6).

Bone pain

Pain associated with primary tumor or bone metastases is a fairly frequent form. The incidence of bone metastases in cancer is high, in the range of 60-80% of cases. Bone metastases are more common in patients with breast, lung, and prostate cancer. The presence of primary or secondary bone disease has a significant impact on the quality of life of patients, as it induces pain, reduces the possibility of ambulation, and leads to the appearance of neurological deficits and pathological fractures. Pathological fractures appear in 8 to 30% of patients with bone metastases, especially in patients with myeloma or breast cancer, although this incidence is likely to decline strongly after the introduction of bisphosphonates (see chapter 13). Pain from bone metastases affects 28-45% of patients according to the progress of the disease. Due to its intermittent nature, mainly induced by activity, this pain is difficult to control and is considered a negative prognostic factor (7-9).

a) Clinical presentation and diagnosis

The most common sites involved are the vertebrae, pelvis, ribs, femur, and skull. The pain develops insidiously and gradually. It is well localized, prevails at night, and is induced by the load on the bone structure involved. Pain at rest may be moderate, but is generally exacerbated by different movements or positions. This pain, defined as incident, is very difficult to control due to its temporal characteristics (see chapter 9). It can also be associated with radiated pain, muscle spasm, or paroxysmal pain when there is also a nervous compression, as it occurs in vertebral syndromes. The dorsal vertebrae are most frequently affected. In many

cases, mechanical compression is due to the growth of vertebral metastatic deposits. The mass can grow posteriorly and extend to the epidural space. The pressure is transmitted to the marrow, resulting in mechanical damage, ischemia, and venous stasis. Compression leads to a progressive neurological deficit below the lesion. The onset is progressive and insidious, with vague lumbar pains, weakness in the lower limbs, and dysaesthesia. Radicular pain is unilateral at the cervical and lumbar level, but bilateral at the thoracic level. The pain is exacerbated by supine position, flexion of the neck, uplifting of the limbs, coughing, local pressure, or lifting. Weakness, sphincter disturbances, and loss of sensitiveness are rare initially, but develop afterwards to an established framework. Cervical lesions cause tetraplegia, while thoracic lesions lead to paraplegia. Lumbar compression, on the other hand, results in cauda equina syndrome (see chapter 25h).

In addition to pain, symptoms associated with hypercalcemia, such as nausea, vomiting, anorexia, constipation, weakness, dehydration, polyuria, and mental confusion, may be present. Bone lesions can be diagnosed by a variety of methods, such as standard radiography, scintigraphy, tomography, and magnetic resonance. With conventional radiography, there is a need for a 40% bone density variation to identify a bone metastasis. Scintigraphy has superior diagnostic capabilities (requiring 10% density variation), but is poorly specific, as some benign conditions may provide false positives. Tomography is certainly more sensitive, while myelography, even if more invasive, allows the identification of the lesion for a certain extension of the spine. Finally, magnetic resonance outlines the details and allows a differentiation between traumatic events, osteoporosis, pathological fractures, compressions, paravertebral extensions, and marrow integrity. Data derived from these investigations should be interpreted in the context of the clinical picture (10).

b) Pathophysiology

There is a dynamic balance between absorption and new bone formation. These phenomena are mediated by osteoclasts and osteoblasts, probably with the mediation of mononuclear cells. Osteoblasts synthesize a matrix that will undergo mineralization. A similar sequence of events occurs in the cortex, but the absorption cavity is a tunnel that runs along the length axis. Most of the activity takes place in the trabecular bone, because of the larger surface available. The coupling of the remodeling phases, the bone resorption, the formation of a new matrix, and the subsequent mineralization, are maintained in equilibrium under normal conditions. The remodeling affects about 15% of the bone each time, but

there may be an increase in the exchange in various conditions. When cancer cells are attracted by chemotaxis on the bone surface, the normal replacement process is disturbed, resulting in a decoupling of events resulting in a loss of bone architecture. The breakage of the trabecular continuity leads to a structural weakness and a reduction in the resistance to compressive and bending forces. An increased osteoclastic activity is stimulated directly or with the intermediation of some factors released by the neoplastic cells, which favor the phenomenon of bone erosion. The mechanisms responsible for osteoclast activation differ according to the type of tumor. In myeloma, bone resorption predominates, due to the secretion of substances that predominantly activate osteoclasts. On the contrary, in prostate cancer an osteoblastic activity that involves a sclerotic bone attitude prevails. These characteristics can also be found radiographically. Finally, some tumors present intermediate and mixed characteristics, even though osteolytic attitudes often prevail.

Pain can be partly caused by the proliferation of osteoclasts. In order to absorb bone, osteoclasts must maintain an acidic environment capable of activating pH-sensitive ion channels and vanilloid receptors in sensory neurons. As soon as the neoplastic cells fill the medullary space, the consequent apoptosis contributes to the maintaining of this acidic environment. Mechanical stress produces distortion phenomena with excitation of the mechanical fibers present in the periosteum. This produces pain induced by movement, due to the mechanical distortion therein. Although the periosteum is densely innervated, the bone marrow and the mineralized bone receive the largest contingent of sensitive and sympathetic fibers. Therefore, patients often perceive pain when the disease is confined and there are no signs of periosteal involvement. With the loss of bone architecture, pain worsens and intermittent pain episodes appear spontaneously or only upon loading (11).

The etiology of pain due to the bone localization of the disease depends on multiple factors. A fundamental role is played by the increase of nociceptive impulses, due to the presence of neoplastic tissue on the sensory endings through distension and perivascular endosseous destruction. Recently, it has been shown that the periosteum and the mineralized bone are richly innervated by primary Aδ afferents – able to express the neuropeptide Y (NPY) and the vasoactive intestinal peptide (VIP) – and by C fibers, able to express receptors for the peptide gene-related to calcitonin (CGRP), vanilloid receptors (VR1), and sympathetic fibers. Tumors that invade the bone interact and activate the primary afferents, alter the osteoblast-osteoclast balance, and induce a pronounced inflammatory response (12). The presence of peritumoral outbreaks

produces the activation and release of chemical mediators with edemigenous action. Probably, the same neoplastic cells produce chemical intermediates with nociceptive and osteoclastic action. The reabsorption and regulation of osteoclastic activity are influenced by the RANKL-RANK-OPG system and by substances such as pTH, PTHfP, 1-25 (OH) 2D3, cytokines, and growth factors (13).

Experimental data from animal models has allowed exploration of a clinical situation previously described simplistically in terms of mechanism, such as deep somatic pain. In these animal models, sarcomatous cells are implanted and cemented in the intramedullary space of the femur. With the growth of the tumor inside the bone the number of osteoclasts increases and the bone destruction appears evident radiologically. At the medullary and ganglia levels neurochemical reactions, typical of central sensitization phenomena, are observed. In particular, an increased expression of the enzymes that induce a glial proliferation has been highlighted, which only appears on the side where the neoplastic lesion was induced. In fact, an overexpression is observed both of the c-fos immunoreactive neurons, a phenomenon associated with chronic pain states, and of dynorphine, a pro-nociceptive peptide, widely expressed in inflammatory models. Furthermore, an important glial reaction typically observed in neuropathic pain models is observed. Therefore, the mechanism responsible for bone pain seems quite specific, differentiating itself from inflammatory and neuropathic pain due to the different neurochemical profiles seen at the medullary level. The pain could be produced by a series of hyperalgesic factors, such as prostaglandins and endothelins, produced by neoplastic cells. In addition, macrophages, strongly present in the neoplastic mass, produce factors such as tumor necrosis factor and interleukin-1, which are able to excite the peripheral neuron. It has also been shown that, as a result of bone resorption, the growth factors contained in the mineralized bone are released by activating equally the afferent fibers contained in the bone (14).

The pharmacological response has also been studied with respect to those observed with experimental inflammatory models. With the same level of experimentally detectable pain intensity, opioids are able to control pain effectively in both models, but the effective dose required in the bone metastasis model was 10 times higher than the dose needed to achieve similar painful behavior in the inflammatory model. This observation explains the reduced sensitivity to opioids in pain induced by bone metastases (15). The presence of a neuropathic mechanism also in

patients with bone metastases could be associated with this type of response (16).

Bisphosphonates are the standard therapy for the prevention and treatment of bone metastases and their complications due to their mechanistic effect. These substances inhibit the maturation and functioning of osteoclasts and determine their apoptosis. Thanks to this inhibitory effect on bone resorption mediated by osteoclasts, bisphosphonates have been developed for the treatment of osteolytic bone metastases, such as those typical of multiple myeloma and breast cancer. However, osteoblastic lesions can also lead to an increase in bone turnover, and bone resorption markers are significantly increased even in patients with advanced prostate cancer, a tumor characterized by predominantly osteoblastic metastases (17) (see chapter 13).

Neuropathic pain

The term neuropathic pain is defined as the type of pain, due to a disease or a lesion, which is associated with an alteration of the function of the somatosensitive system at the level of the peripheral and/or central nervous system, in the absence of a stimulation of the nociceptors by a tissue trauma (18). The pathophysiology of this phenomenon is quite complex. Following a peripheral lesion the A-δ and C afferent fibers become abnormally sensitive and develop a spontaneous pathological activity leading to peripheral sensitization. This results in an overexpression of sodium and calcium channels and the release of various receptor proteins and growth factors from degenerate fibers. This activity causes secondary alterations in the central processes leading to a spinal cord hyperexcitability and with consequent central sensitization. The descending pathways lose their balance of control, with a prevalence of excitatory activity over the inhibitory one, further exacerbating the state of bone marrow excitement (19) (see chapter 7).

Depending on the site of the lesion, it is generally classified either as “peripheral neuropathic pain” when the dysfunction affects the first neuron or as “central pain” when it originates from dysfunctions in the central nervous system. The various signs and symptoms of neuropathic pain are combined in different clinical pictures. Particularly in pain due to damage to nerve structures associated with disease progression, quite complex frameworks are observed, mostly in a mixed frame, with variable aspects over time due to the dynamism of lesions and signs of the manifestation.

These observations explain both the heterogeneity of the clinical pictures, and the individual responsiveness to commonly used drugs, such

as opioids and analgesic adjuvants, represented by fairly inhomogeneous classes of drugs. In fact, patients with neuropathic pain have shown less responsiveness, even if not absolute, to opioids and a greater propensity to develop side effects (20).

a) Pathophysiology

The relationship between the pathological mechanism of pain and the symptoms of neuropathic pain is quite complex. For example, sensitized C-nociceptors can produce spontaneous and evoked pain. Pain can be caused by different mechanisms, as in the case of the allodynia present in both peripheral and central sensitization. In the same patient both evoked and spontaneous pain can be present simultaneously. Once evoked, pain may persist for hours making the distinction between evoked and spontaneous pain difficult. In some cases of particular severity and frequency of stimulation, the evoked pain leaves a persistent sequela which makes it difficult to differentiate from spontaneous pain. Often the phenomena are indistinguishable regarding the presence of signs and symptoms typical of neuropathic pain (21). From the neurophysiological point of view possible examples of the pathogenic mechanisms of neuropathic pain that arise after damage of the first neuron follow:

1) Peripheral nerve lesions, both demyelinating and axonal, are able to make peripheral nerve fibers hyperexcitable. One example is the hyperexcitability of the regenerating nerve endings after an axonal lesion of the nerve. This hypersensitivity manifests itself as a result of chemical, mechanical, or thermal stimuli, which probably generate pain due to the formation of ectopic sites in the injured areas as well as at the level of the sensory ganglion.

2) The first nociceptive neuron can give rise to ectopic discharges even after adrenergic sensitization phenomena. The adrenergic stimulus can be induced by an increased efferent sympathetic activity or by the normally circulating catecholamines.

3) Spontaneous activity in C nociceptors is responsible for continuous pain and above all for the sensitization of spinal neurons. The spontaneous activity of myelinated A fibers (which generally carry harmless sensations) generates spontaneous paresthesias and, after central sensitization, dysaesthesia and pain.

4) The second neuron can be of two types: specific, with exclusive connections with nociceptive neurons at the level of the posterior horn in the spinal cord, or convergent, connected both with nociceptive fibers and fibers that normally tranposrt tactile sensitivity (Aβ). The hyperexcitability of the neurons of the posterior horn follows the phenomenon denoted by the term "spinal cord hypersensitivity", caused by the increase of afferents coming from the first neuron. The events that occur at the spinal level are represented by an inhibition exerted by the inhibitory GABA system and by the descending serotonergic and adrenergic inhibitory systems, by a possible reduced efficacy of opioids at the receptor level, and by the activation of NMDA receptors. Therefore, the noxious stimuli that reach the dorsal horns increase neuronal excitability with an exaggerated response to subsequent stimuli.

5) At peripheral level a sensitization of adjacent neurons can be observed for the antidromic release of algogenic substances.

6) Glia has traditionally been considered a connective structure for neurons. In the last decades a more relevant function has been attributed to glia, concerning neuronal homeostasis and the immune response, and above all it has been recognized to have a role in the modulation of pain. Following activation, glia initially produces a variety of neuro-excitatory substances, including interleukin 1 and 6 (IL1, IL6) and tumor necrosis factor, particularly following experimentally induced nerve lesions. The activation of toll-like receptors (TLR) produces a pro-inflammatory cascade similar to that documented with interleukins. Knock-out studies, in animals without such receptors, or the use of antagonists for such receptors, have produced the prevention of the development of allodynia in experimental models of neuropathic pain, confirming the role of these receptors in the phenomena of hyperexcitation. Opioids are also able to induce analgesia and at the same time to activate glia, through the overexpression of the TLR. Therefore glia may condition opioid analgesia by reducing its flow rate or inducing tolerance and addiction (21).

b) Clinical aspects of neuropathic pain

About 20% of cancer patients have neuropathic pain, although the definition has not been substantial in most clinical trials (22). Most

mechanisms are multiple and neuropathic pain is a relative component (23). It is a fairly heterogeneous entity and groups together many painful forms characterized by common denominators represented on the one hand by damage of peripheral and central nervous structures and on the other by pain and negative sensory signs, characterized by partial or complete sensory deficits, and/or positive signs, including pain, dysaesthesia and paresthesia.

Among the peculiar characteristics of these clinical pictures is the presence of pain or disease caused by a non-harmful stimulus. Allodynia is the term used when a normally non-painful stimulus is able to cause pain. Observed in the patient with neuropathic pain is both a low-threshold A-β mechanical allodynia, where the pain-inducing stimulus is mechanical (very light, skin skimming), and a high-threshold mechanical allodynia in which the A-β fibers do not seem to be involved. In this case, the allodynia could be mediated by nociceptive afferents that have a reduced threshold compared to the norm, due to, for example, the antidromic release of algogenic substances. Thermal allodynia, from hot or cold, is evoked by normally non-painful thermal stimulation and is often associated with static mechanical allodynia.

Allodynia has always been considered a cutaneous phenomenon, but its existence has been postulated even in deep tissues, such as in bone pain (24) (see chapter 9). Allodynia reflects a central phenomenon of sensitization, gives a response to impulses that start in the myelin fibers with a large diameter, and is associated with a slow summation of stimuli.

Nociceptor: receptor preferentially sensitive to a painful stimulus or to potential stimuli if prolonged

Harmful stimulus: stimulus capable of damaging tissues

Pain: an unpleasant emotional or emotional experience associated with current damage or tissue potential, or described as such.

Central pain: pain caused by an injury to the central nervous system

Peripheral neuropathic pain: pain caused by a lesion or dysfunction of the peripheral nervous system.

Paresthesia: abnormal, spontaneous, or evoked sensation

Dysesthesia: annoying, spontaneous, or evoked anomalous sensation

Allodynia: pain due to a harmless stimulus
Pain maintained by the sympathetic (CRPS/reflex sympathetic dystrophy): painful syndrome with burning pain, allodynia, insurgent hyperpathy after a traumatic injury, often associated with vascular dysfunction, sweat and trophic
Hyperalgesia: increased response to a harmful stimulus
Hyperpathy: abnormal and prolonged reaction to a repetitive stimulus
Neuralgia: pain in the distribution of a nerve
Neuropathic pain: pain started due to a lesion or dysfunction in the nervous system
Neuropathy: alteration of the function of one (mononeuropathy) or more (multiple mononeuropathy) nerves, or of diffuse and bilateral nerves (polyneuropathy)

Table 2. Terms and definitions concerning neuropathic pain, according to the IASP.

Hyperalgesia can also be triggered by mechanical and thermal stimuli and appear in different ways. It might appear that the difference between allodynia and hyperalgesia is clear, but often in clinical practice it is quite difficult to differentiate the two signs. When present, allodynia and hyperalgesia can be quantified by measuring their intensity, duration, stimulation threshold, and area. Hyperpathy is a variant of hyperalgesia and allodynia in which the pain is explosive and particularly intense, evoked by a harmful stimulus in a cutaneous area with an increased sensory threshold. Pain can also be evoked by a normally harmless stimulus, or by both types of stimulus. Pain is often perceived after a certain delay and appears particularly after repeated stimulations. Hyperpathy is always accompanied by the injury of nerve fibers.

The phenomenon known as “wind-up” appears to be dependent on central phenomena following a response by spinal neurons to repeated stimuli by the C fibers. “Wind-up” like pain or abnormal temporal summation reflects an increased activity and is observed in some forms of neuropathic pain after the repeated application of painful and painless stimuli in the same area at intervals of less than three seconds. The

stimulus can be tactile, thermal, or electric. Patients with "wind-up" like pain typically exhibit A-β mechanical allodynia. Instead, the term aftersensation indicates the persistence of pain beyond the end of pain stimulation (25).

In the forms maintained by a hyperactivity of the sympathetic system, changes in skin color, sudomotor modifications, edema, and changes in nail and hair growth are observed. Motor disorders such as tremor, dystonia, and force reduction in various muscle groups can be associated with stiffness and joint effusion.

The distribution of these alterations in sensitivity may be of the dermatomeric type, thus affecting the distribution territory of a peripheral nerve, or may have another distribution (glove or sock). It can involve a single nerve (mononeuropathies), more nerves (polyneuropathies), a nerve plexus (for example, thoracic outlet syndrome), or the roots or ganglia (post-herpetic neuropathy). Particularly complex is the clinical picture of post-herpetic neuropathy in which there are different types of pain and sensory abnormalities. The pain can be burning, spontaneous and continuous, or deep and dully persistent, or even spontaneous and excruciating, and is accompanied by allodynia and hyperpathy.

Neuropathic pain can occur in various ways as spontaneous and continuous, spontaneous and paroxysmal, or intermittent, abnormally evoked (from touch, from movement). The pain evoked by a stimulus (tactile, thermal) can be abnormal and assumes the characteristics of allodynia, hyperalgesia, and hyperpathy. Pain can be felt both superficially and profoundly. In deep tissue it is often described as "cramping form" or able to tear, while on the surface it is often described as "burning" or "pungent". The paroxysmal episode is usually perceived as "electric discharge" or "excruciating". This nomenclature is often used to diagnose neuropathic pain, even if there is currently no certainty, but only the probability of the diagnosis of neuropathic pain as opposed to nociceptive pain. In lesions of the nervous system caused by the spread of cancer mass or secondary localizations, both neuropathic pain and neurogenic nociceptive pain can be found, due to inflammation of the perinervium, generally in the compressive forms.

c) Classification of neuropathic pain

There is currently no validated means that provide criteria for diagnosis. In fact, neuropathic pain is not a single entity, but is represented by a group of heterogeneous conditions that differ in etiology, localization, and symptoms (26). Diagnosis often rests on the physician's experience and on an overall assessment of the clinical and instrumental examination.

Numerous tools – such as the Neuropathic Pain Questionnaire (NPQ), the complete and synthetic form (NPQ-SF), the Leeds assessment of neuropathic signs and symptoms (LANSS), the Neuropathic Pain Symptom Inventory (NPSI), the DN4 (douler neuropathique in 4 questions), Paindetect (PD) – have been proposed to evaluate the different symptoms-signs of neuropathic pain (27). Most of these tools have allowed the discrimination and quantification of the most relevant dimensions of neuropathic pain and have also been partially sensitive to treatment. In recent years, a more possibilistic concept has prevailed, taking into account the variability of clinical pictures according to a hierarchical classification that characterizes the syndromes as definite, possible, and unlikely (28, 29).

This concept is combined with the therapeutic aspects, so that neuropathic pain is not a priori insensitive and refractory to opioids, but presents a range of individual responses. Certainly neuropathic pain is a therapeutic threat because it requires higher doses of opioids, longer stabilization times, and a higher need for therapeutic modifications, including opioid substitution (30).

More recently, specific neuropathic pain classification criteria have been offered to standardize the diagnosis (neuropathic pain special interest group, NeuPSIG grading system) (31) (table 3).

1) Pain with a distinct and plausible anatomic distribution
2) History of a lesion or disease that affects the somatosensitive system
3) Confirmation tests that demonstrate the presence of positive or negative signs in the area of innervation of the lesion (physical examination, quantitative tests)
4) Diagnostic tests confirming the presence of lesion or disease associated with neuropathic pain (imaging studies)

Table 3. NeuPSIG grading system

The presence of points 1 and 2 represents a possibility of neuropathic pain. The presence of 3 or 4 represents a possible diagnosis, definitively confirmed by the presence of 3 and 4 together. Therefore, over time a probabilistic tendency has come to prevail in the diagnosis of neuropathic pain, rather than a binomial characteristic (32). Recently, an algorithm for classifying neuropathic pain in cancer patients has been proposed based on expert judgment (33).

Recognition of a neuropathic component is crucial in terms of responsiveness to analgesics. Indeed, neuropathic pain has always been

considered to be poorly responsive to opioids. The reason probably lies in the fact that the biochemical alterations, with an increased spinal cord sensitivity, are in some way very similar to those observed in the development of tolerance and hyperalgesia induced by opioids (see chapter 19b, c, and d).

d) Characteristics of neuropathic pain in the cancer patient

Compared to those forms that appear more defined, because more related to non-cancer diseases, as in the case of peripheral damage from chemotherapy or post-herpetic neuropathy, the mixed forms, associated with a nociceptive component, are certainly the most frequent and the least definable (34). These clinical presentations tend to change over time, probably as an expression of the clinical evolution of the causes that have led to their onset. In the advanced stages of disease negative signs prevail, probably due to a greater involvement of the nervous structures. In pain due to a spinal lesion the components that can be found are multiple: a central pain (from deafferentation) below the lesional level, a radicular pain in the dermatomeric area corresponding to the damaged roots, a mechanical, somatic deep component in the vertebral area affected, and finally also a visceral pain in diffuse or focal form to the abdomen or in other places.

From the point of view of the dynamic transformation, Pancoast's syndrome is paradigmatic. The progression of lung disease initially leads to an infiltration of the brachial plexus with irritative responses, thus generating a somatic type of pain, like a nervous trunk without clear neurological signs. As the disease progresses, the lesion is identified as brachial plexus injury with a reduction in function. Pain manifests itself later in the preponderant form when the pulmonary cancer invades the paravertebral region, the conjugation holes, and the epidural space, generating a parallel Horner's syndrome. Pain, really intense, superficial and burning, typically appears in the dermatomes of the first two thoracic roots and the lower cervical roots, associated with other clear neurological signs.

There are forms due to tumor growth, primary or metastatic, or due to surgical treatment, radiotherapy, or chemotherapy. Finally, there are forms that, although not directly caused by the tumor or treatment, have a link with the disease.

- Neuropathic syndromes due to cancer

Secondary neuralgias of the trigeminal are frequent in tumors of the middle and posterior cranial fossa, in meningeal infiltrations, and in those

of the cranial base near the emergence of the roots in the peripheral path of the three branches. In the clinical evaluation, negative neurological signs and pain characteristics are important, continuous and non-accessory accompanied by paresthesias, which helps in distinguishing secondary trigeminal neuralgia from essential neuralgia. When lesions affect the area of the jugular hole, secondary neuralgia of the glossopharyngeal appears with pain extended to the pharynx, at the base of the tongue (with paralysis of the vocal cords), at the ear and the mastoid region, and at the nape and neck. Also in this case, negative signs and motor damage depose for the secondary form and not for essential neuralgia.

Pain due to neuropathic radiculopathy (i.e., from spinal roots injury) is characterized by a dermatomical distribution and is caused by an invasion of the conjugation hole by extravertebral neoplastic masses, by epidural masses, or by leptomengeal metastatic infiltrates. The meningeal forms generally present a complex and multifocal clinical picture, characterized by radiculopathy, cranial neuralgia, headache, or ataxic or hemiparetic signs. In clinical cases of radiculopathy it is always useful to resort to magnetic resonance as a diagnostic tool, because from other radiological investigations it is frequent to obtain negative or at least dubious answers.

Cervical plessopathies generally affect the auricular region, the neck, and the upper part of the back, almost always being associated with Horner's syndrome and the paralysis of the hemidiaphragm. In cervical plessopathy, a magnification of metastatic lymph nodes (mammary neoplasms), lymphomas, and progression of the pulmonary neoplasm (Pancoast's syndrome) are often found as causes. In this latter pathology Horner's syndrome appears when the mass, reaching towards the column, involves the sympathetic chain.

The causes of lumbar plexopathies are due to the extension of colorectal carcinomas or of the uterine cervix, sarcomas or lymphomas, or neoplasms of the kidney, as well as distant metastases from breast and lung cancer. When the upper part of the plexus is affected, pain appears in the lumbar, abdominal, iliac crest, or hip. In the forms that affect the lower branches, the symptomatology is localized to the gluteus, perineum, and lower limbs. The evolution of the presacral masses generally involves the sacrum with neurological signs at the perineum and the sphincters. Sciatic neuropathies may occur from expanding masses to the thigh (bone and muscle tumors). Intercostal neuropathies are consequent to infiltration by pleuro-pulmonary tumors or to costal metastases. These are mixed forms in most cases. Central pain is quite rare, although vascular lesions can frequently coexist.

- Iatrogenic or accompanying forms

There are many forms related to collateral events: post-herpetic neuropathy, peripheral neuropathy by chemotherapy, post-surgical neuropathies, phantom pain of the amputee, myelopathies, plexopathies, and actinic neuropathies. In some cases, radiculopathies are produced by the epidural and subarachnoid administration of neurotoxic drugs. At the origin of post-mastectomy syndrome there appears to be an injury to the intercostal-brachial nerve which generates painful symptoms in the chest, arm, and medial face of the arm.

Other post-surgical forms are lateral-cervical neuropathic syndrome and post-thoracotomy syndrome, which typically occur at least three months after surgery. They affect the hemithorax operated upon and remain a long time before disappearing slowly and spontaneously (17).

Regarding the actinic forms, subacute myelopathy may arise after radiotherapy of extraspinal neoplasms, such as head and neck cancers, or Hodgkin's disease. Transient myelin damage is responsible for electrical discharge pain extended to the spine and extremities. Generally it regresses within a year. The chronic form of myelopathy is much more severe due to painful symptoms and signs of loss. The first to appear, after an interval of several months, are signs of myelin damage or necrosis of the white substance, followed at a distance from those of ischemic damage. From a clinical dermatomical form of localized myelopathy, it passes to a Brown Sequard's syndrome with motor and extrapyramidal signs on one side and contralateral sensory deficits. Thoracic and axillary irradiation causes brachial plexus neuropathy, usually accompanied by intense pain and sensory and motor deficit signs (17).

Peripheral pain polyneuropathy may be a complication of a chemotherapeutic treatment. Although the neuropathic symptoms are often modest, neuropathy is the third most frequent and problematic adverse effect. The pathophysiology is poorly known (18). The high potential neurotoxicity drugs are platinum derivatives, taxanes, bortezomib, vincristine, thalidomide, and protease inhibitors. No obvious risk factors have been found, except for a previous history of neuropathy. The consequent disability forces a reduction in the dosage of chemotherapeutic agents or even the suspension of therapy, with a consequent increase in morbidity and mortality linked to cancer. 68% of patients receiving chemotherapy develop the neuropathy within the first month after the end of the cycle, 60% within three months, and 30% show neuropathy again at 6 months or more after the discontinuation of treatment. Chemotherapy-induced neuropathy usually occurs at the beginning of treatment with distal sock and glove distribution that can evolve into pain. The most

frequent neuropathic symptoms are tingling (71%), numbness (58%), sensitivity disorders (45%), and pain (40%). Based on the type of chemotherapy, the evoked mechanical hypersensitivity and cold allodynia can be associated with spontaneous pain.

In reality, cancer pain in its widest sense is a very complex phenomenon, in which even the humoral, inflammatory, genetic, and plastic responses of the nervous system are responsible for a series of biochemical reactions that have many similarities with the molecular alterations typically generated by a nerve injury. Paraneoplastic neuropathies occur with pulmonary microcytomas and with ovarian and mammary cancer. Dysesthesia and pain begin distally and asymmetrically. It is a purely sensory neuropathy involving ganglion cells in which gliosis, inflammatory infiltrates, and cell death are evident. There was a close correlation between this syndrome and the plasma levels of a type I IgG antineuronal nuclear antibody known as anti-Hu. The cytokines, produced abnormally and invariably released during neoplastic disease or during the typical post-chemotherapy period, play a fundamental role in the neuroinflammatory response, often difficult to distinguish from both inflammation and traditional neuropathic pain. Referring to paraneoplastic syndromes, for example, there is an autoimmune inflammatory situation in relation to the nerve in which there is strong immunological mediation.

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CHAPTER NINE

BREAKTROUGH PAIN

Breakthrough pain (BP) is defined as a transient increase in pain intensity occurring in a situation of relatively good pain control for most hours of the day in patients generally treated with analgesics given at regular intervals (1). The presence of BP affects the quality of life, the duration of sleep, and the degree of functionality, and is generally accompanied by a considerable degree of psychological suffering, with anxiety and depression, and dissatisfaction with treatment (2). The prevalence is quite variable in the literature according to the setting and the stage of the disease, with about 70% of patients on chronic opioid treatment exhibiting important fluctuations in pain intensity (3).

BP subtypes

The etiology of BP in cancer patients is predominantly cancer itself. Most patients report from one to four episodes, with an average duration of 30-60 minutes and a somewhat variable latency of occurrence. Almost all patients present exacerbation of pain at the same site as of background pain (4). Different mechanisms, somatic, visceral or neuropathic, can also characterize this form of pain (see chapter 8). For example, a paroxysmal pain with a short latency typically recognizes a neuropathic type mechanism, especially at the vertebral level. The onset of symptoms that are a prelude to spinal cord compression is often insidious. The pain is exacerbated in the supine position, by the bending of the head, by the lifting of the limbs, by coughing or by local pressure. Also peripherally, a lesion of the nerve fibers can induce an entirely unpredictable electrical-burning pain, or be induced by simple skin contact. Abdominal colics, generally attributable to alterations in peristaltic coordination, often observable by sudden distension of ducts or loops, associated with a downstream obstruction, are of biliary, intestinal, or urinary origin, depending on the affected area. Injuries to the oral cavity with mucositis or skin lesions due to infiltration of the soft tissue may cause painful events due to mastication, swallowing, or simple contact. Finally, some muscle

movements, such as spasms or myoclonus, can be painful and unpredictable. The most important categories and sub-groups are shown in table 1.

a) Spontaneous – unpredictable – idiopathic pain (60%)
b) Predictable pain (40%):
- voluntary (induced by movement, or by touching the skin or swallowing)
- not voluntary (induced by unexpected causes)
- consequent (post-prandial)
- procedural (anticipated)

Table 1. Main categories of BP

The most common form of BP is represented by incident pain, due to the movement associated with bone metastases, and includes about 40% of the episodes described as BP. It is generally predictable or avoidable, as it is induced by movement or by a well-identified event, such as swallowing. This type of pain is difficult to solve and is one the most relevant negative factors for pain outcomes. It strongly affects daily activity, because it often limits physical activity, even in bed. Continuous pain may be absent or moderate at rest, but it is exacerbated by load on the affected bone, by some movements or changes in position, or by coughing or even deep breathing.

The idiopathic form does not recognize an identifiable cause and is generally characterized by events that arise more slowly and are more prolonged. Thus, onset and duration may be longer (5).

In some cases the presence of BP may be an expression of inadequate pain control, and strictly speaking it should not be considered as such. For an adequate diagnosis of BP, it is necessary to optimize the background analgesia and avoid a pain that is not effectively controlled being erroneously considered BP. From a clinical point of view, a distinction must be made between episodes that appear during the opioid dose titration phase, which are to be ascribed to an ineffective current dosage, and episodes that appear in patients with otherwise controlled pain. Frequent exacerbations of painful intensity during the day may be a sign of inadequate analgesic treatment. When pain intensity becomes more severe with frequent peaks, pain can be treated by increasing the dose or reducing the dose interval between doses until a more advantageous balance between analgesia and side effects is achieved. Although an optimization of the background

analgesia is able to reduce the number and intensity of the episodes, the phenomenon will remain present (6). This approach is fundamental in the treatment of abdominal BP of visceral origin, for example postprandial BT pain, because optimization of background analgesia is able to eliminate the phenomenon in a large proportion of patients (7).

Finally, pain can be induced by very painful and therefore predictable procedures, which determine a short duration pain limited to the execution and in the immediately following period, as for the dressing of wounds or sores, or prolonged immobilization for the simulation of a program of radiotherapy.

Thus, there is a certain heterogeneity of mechanisms that can underlie a sudden worsening of the intensity of pain during the day, which in some cases will require interventions aimed at the basic mechanism rather than the control of the event, or better timed in relation to foreseeable events.

Assessment

For an accurate evaluation of BP, questionnaires have been used that substantially reproduce a diagnostic algorithm (8, 9). The key points are the relationship with the background pain, the characteristics of onset, frequency, intensity of the painful peak, location, quality, duration, causes and painful mechanisms, predictability, effectiveness of the drugs used, and satisfaction with the timing of efficacy (10). From the clinical point of view, the most important issue is on the making of a clear distinction between background pain oscillations, normally present during the day, and painful peaks of such intensity as to require a specific treatment. In fact, in many studies this distinction was approximate and probably led to mistakes in the selection of patients to be submitted to a clinical study on the drugs used for BP.

It has been observed that in patients trained in the use of drugs as needed, the most frequent pain intensity to induce the patient to request a drug when needed was 7/10 on a numerical scale. On the other hand, patients considered a treatment effective when pain intensity returned to baseline levels (3-4/10), or decreased by about 50% (11).

The number of episodes per day conventionally considered acceptable is 1-4. Assuming a duration of 30-60 minutes, a drug could be administered to cover these hours, if for the rest of the day the pain is kept under control. This concept is not always extensible to pain-induced movement associated with bone metastases, in which every movement can produce pain such that the patient limits his mobility. All possible efforts must be made to find the best background analgesia to enable better

mobilization (6). Paradoxically, in the most advanced bedridden patients, this form of predictable pain induced by movement is less frequent due to reduced physical activity (12). The elements necessary for an overall assessment of the BP are presented in table 2.

Do you have episodes of sudden increase in pain intensity?
How many episodes per week/per day?
How long does it develop over?
How long does it last?
What intensity does it reach?
Is it equal or different from background pain?
Does it appear spontaneously or is it induced by some activity?
Does it appear at the end of analgesic dosing?
What impact does it have on daily life?
Do you avoid doing something in this case?
What allows you to reduce pain?
What treatment and how long has it been taken?
Is it effective?
Which drugs and which doses?
Are they effective?

Table 2. Elements to be known for an appropriate assessment of BP

Management of BP

Before planning any more or less intensive treatment, it is very important to determine the level of quality of life of the patient, his chances of ambulation, and the expected survival, since the approach can be totally different. Limiting movements may have a completely different meaning for patients who are able to walk than for patients with an expected survival limited by advanced disease, often bedridden due to precarious conditions. In fact, some alleviating factors can be identified and used only at certain levels of performance. Furthermore, a series of different treatments – such as facilitating defecation, reducing the amount of intestinal gas, the use of antacids, or the massage of the painful sites – can be useful in some circumstances.

Radiation therapy is the main treatment for bone metastasis pain and should therefore always be considered in the presence of incident pain associated with bone metastases. A background pain control will reduce the frequency and intensity of painful exacerbations. Prosthetic aids can be useful in incident pain in the presence of fractures or imminent fractures.

A stabilizing, invasive, or minimally invasive (cementoplasty) intervention (chapter 20) can be decisive in improving the quality of life of patients with a strong functional limitation, but in the absence of visceral disease and therefore with a reasonable survival. For the more specific indications and problems related to radiotherapy, the use of radioisotopes, and orthopedic and rehabilitation interventions, please refer to more specific textbooks.

- General considerations

In some cases the presence of frequent and high intensity episodes masks an inadequate control of background pain. Such situations can be addressed with a modification of the therapeutic regimen that will be considered effective when no more than two or three episodes per day appear. In some cases pain is apparently well controlled at rest, but the patient is practically immobilized in bed or forced to limit his physical activity considerably, for example in patients with bone metastases, particularly at the vertebral level, when even a minimal load can induce a painful reflex reaction such as to suspend the movement that was intended to be performed. In practice, the patient does not have pain at rest, but this can violently appear with movement at high intensity. In some cases it occurs not immediately but after a certain physical activity. Therefore the development of BP may be different. The development of incident pain in some clinical situations is so rapid that no medication has a latency of action able to overlap temporally with respect to the event. The state of neuronal excitation present at the spinal level that resembles the observable one in neuropathic pain and that is less responsive to opioids is described in chapter 8.

In an attempt to optimize baseline analgesia, an increase can be made in the opioid dose by 30-50% of the dose that is sufficient to control pain at rest or that in any case ensures an accurate titration up to the achievement of an acceptable balance. This approach may improve the possibilities of movement without inducing important side effects. However, there is a risk of causing side effects if the therapeutic window is restricted. In this case, the increase should be suspended and the use of drugs as needed should be left to the discretion of the patient (5). In very experienced hands, opioid performance can be improved by substituting the opioid with a more effective alternative for that patient.

- Non-opioid drugs

The use of non-steroidal anti-inflammatory drugs (NSAIDs) may be effective in reducing the number of episodes of BP, due to the additional

analgesic effect on opioids, such as in mucositis or in incident pain, even if this aspect has never been explored and NSAIDs use is exclusively anecdotal. In a weak study, intravenous flurbiprofen provided a more rapid meaningful pain relief in comparison with oral morphine (13). However, this finding is disputable, as the anti-inflammatory drug was given over 30 minutes as an infusion and it is quite difficult to recognize an effect after about 15 minutes (just after the infusion of half dose).

In any case, NSAIDs can be useful, if not administered regularly, as drugs when needed, with the fastest formulations (fast, sublingual, or parenteral). There are patients in whom NSAIDs exert a formidable analgesic effect, even as needed drugs, with the fastest formulations.

Ketamine by nasal or sublingual transmucosal route has been used with some success in doses of 10-20 mg (14) (see chapter 13). The main problems are related to the difficulty of use due to the possibility of the appearance of side effects and the exclusive hospital availability. The main advantage is that the efficacy is independent of the dose of opioids administered for the baseline pain. In patients receiving high doses of opioids for background pain, the approach is quite complex because a high level of tolerance requires very high doses of opioids for BT. However, ketamine is a complex drug, which requires expertise. Safety issues related to psychomimetic effects, irritation of mucosa, and the occurrence of possible cognitive disturbances are of concern.

The spinal route of administration of opioids, but especially of local anesthetics, can be decisive in the more complex cases related to an incident pain (see chapter 20).

While the role of bisphosphonates in bone pain control and the reduction of skeletal complications in patients with bone metastases is well established, the effect in preventing or reducing incident pain episodes is unclear. Episodes of neuropathic pain with shock-like characteristics can be alleviated or reduced in number by the use of adjuvant drugs (see chapter 13) active on the nervous system. Some predictable episodes, such as those involved in moving the patient for the changing of dressings, hygienic maneuvers, or minor interventions, should be prevented by mild sedation with midazolam, propofol, or ketamine. Antitussigen drugs, miolitics, and laxatives can finally be useful in some specific eventualities in which the specific precipitating events are well recognizable.

Nitrous oxide inhalation may produce a rapid analgesia within a few minutes. Recently, it has been shown that self-administered nitrous oxide/oxygen mixture was effective in reducing moderate to severe BP (15), although its use remains controversial (16).

No data exist on non-pharmacological measures, such as relaxing or distraction therapy (16).

- Specific treatment of BP episodes

An additional dose of opioids as needed is the most common means of controlling BP in patients receiving opioids for background analgesia. These extra doses can also be used before the predictable event, such as the performing of certain movements. The choice of the oral route or other methods that accelerate the appearance of the clinical effect will depend on the clinical context, on the feasibility of the proposed method, and on the patient's ability to use, as well as on efficacy, which is therefore not the only parameter to be considered.

Traditionally, an oral opioid such as morphine or oxycodone has been used. The dose to be administered is somewhat variable, although clinical experience suggests the use of a dose of 15% of the daily dose (17). The definitive choice of the dose will depend on the individual characteristics and the response obtained with this standard dosage, in an attempt to find the most suitable dose for each specific case. In the case of incident pain, patients may request a dose capable of causing side effects due to a relative overdose when the painful episode vanishes spontaneously, probably due to a pharmacokinetic overlap of the drug administered as needed and the drug administered at regular intervals (10).

The problem of incident pain is therefore not related to the response to a type of opioid, but to the fact that the doses required for pain to movement may produce unacceptable effects at rest or when the pain disappears spontaneously. The use of oral opioids is in any case characterized by a slow action latency, about 30 minutes, with a peak of action reached after about 45-60 minutes. This method remains very used for ease of use. The slow latency also allows an individualized use in some circumstances in which the daily activity can be modulated in relation to the preventive use of an extra dose of oral morphine, when the pain occurs more slowly and is strictly dependent on the duration of the physical activity.

In most cases, however, BP develops quickly, is unpredictable, and is short-lived. For these reasons the oral route is rather slow and unable to overlap with the development of intense pain in a short time.

The parenteral route is an important alternative, because it allows a significant acceleration of the clinical effect under certain circumstances. The ideal route for rapidity of action is the intravenous route, which allows a rapid change in the plasma concentration of the drug injected. A patient-controlled (PCA) intravenous or subcutaneous administration is a fairly

effective means of allowing a more appropriate dose customization according to the specific needs of the case. The main problem is represented by the technical aspects of the use of pumps, which can limit their use in many subjects, and the costs. The administration of intravenous morphine is particularly effective in terms of timing, providing an immediate and total plasma availability, even if the poorly lipophilic characteristics of morphine require equilibrium times for passage through the brain barrier. The clinical effect is perceptible in 5-10 minutes. For these properties it is used especially during the rapid titration phases in patients with severely painful conditions (see chapter 19a). Doses of 20% of the equivalent dose of morphine or other opioids given at regular times for basal pain are effective and safe (18). For example, if a patient receives 120 mg of oral morphine, 8 mg will be given intravenously (calculated from the conversion of approximately 24 mg orally, that is about 20% of the background dose). Most patients, responsive to opioids, will get pain control in about 5-10 minutes. The use of the intravenous route is growing as many patients have an already implanted permanent system. Subcutaneous administration is equally effective, but the latency of action is slower. The choice of these two routes of administration will be guided by experience, setting, available opportunities, and possible contraindications.

Opioid administration through the mucous membranes is an innovative and less invasive method for rapidly obtaining analgesia. Sufficiently powerful lipophilic opioids, such as fentanyl, are rapidly absorbed transmucosally, reaching effective plasma concentrations within a few minutes. Several controlled studies have confirmed the superiority of this type of administration compared to placebo and oral morphine in terms of efficacy and timing (19). Various transmucosal fentanyl formulations have been introduced (named also rapid onset opioids, ROOs), having different characteristics in terms of plasma availability and diffusion rate. The delivery systems for the transmucosal release of fentanyl are described in chapter 18. The choice of the preparation depends on individual factors and mucosal integrity. A general treatment approach with respect to BP presentation is reproduced in table 3.

a) Short-onset BP treatment in patients receiving opioids for background pain (> 60 mg/day of oral morphine equivalents)

- These patients are opioid-tolerant
- Optimization of the daily dose of opioids given at fixed times
- Use a dose of ROOs proportional to the daily dosage (1/5-6)

b) Treatment of slow onset BP in patients receiving opioids for background pain

- These patients are opioid-tolerant
- Optimization of the daily dose of opioids given at fixed intervals
- Use a dose of morphine or oral oxycodone at the dose proportional to background opioid analgesia (1/5-6)
- If pain is predictable, and the patient is motivated and well informed, the dose may be given 30 minutes before starting activity or eating (according to the principal trigger)

c) Intermittent or recurrent pain, premedication for painful procedures

- These patients are less tolerant to opioids because they may not receive chronic treatment.
- Start with the lowest dose of ROOs if there is no previous data on opioid sensitivity
- The respiratory function (oximetry) must be monitored.
- For very painful procedures, it is necessary to use hypnotic drugs such as midazolam or propofol
- Expert advice

Table 3. Choosing drugs for the main types of BP

- Problems related to the dosage of opioids to be administered as needed

Fentanyl preparations should be used in tolerant patients, i.e., in subjects receiving at least 60 mg/day of oral morphine equivalents for their background pain. In these patients these preparations have been formulated for their immediate availability after transmucosal absorption. This precaution is aimed at avoiding the use in naive patients that can more easily develop side effects, although preventive use for short-term pain diagnostic procedures has been recently enforced even in patients who do not receive opioids for basic pain.

Many observations seem to suggest the need for titration for the dosage of the drug to be administered for the control of BP (20), contradicting in some ways clinical experience that suggests that in tolerant patients, or those already receiving an opioid treatment, it is necessary to provide initial doses proportional to the daily opioid requirement, indicating the level of tolerance of patients. Of interest, starting titration doses were based on a level of tolerance of about 60 mg/day of OM, given for background pain, indirectly suggesting some proportionality. In a real world setting, doses of opioids for BP proportional to those used for background pain were effective and not associated with relevant adverse effects (12). Of interest, the need to titrate has never been determined on the basis of scientific evidence, as a direct comparison between a titration strategy and a no titration strategy has not been performed (21). Although starting with the lowest dose when initiating therapy may potentially increase safety overall, it could itself be problematic. The initial dosing may result in a period of uncontrolled pain or may require the use of repeated doses that could lead to prolonged drug exposure after the BP resolves, undermining one of the potential advantages of the use of a transmucosal formulation over an oral drug (10). If an aggressive dose titration is needed, this may increase the uncertainty, inconvenience, or cost associated with the treatment. Patients under treatment with high doses of opioids will require more attempts, probably unsuccessful, before reaching the required dosage, and this can induce distrust and abandonment of treatment.

Thus, dose titration may reduce the potentiality of fentanyl products in daily activity, particularly in outpatients or at home, as patients may be reluctant to follow a process of titration that can be unsuccessful in the initial steps (10, 22). Indeed, in several studies, proportional doses of fentanyl products were found effective and safe (21). In the only existent comparative study, the use of proportional doses of fentanyl produced more effective analgesia and less drop-outs, while being similarly safe, in comparison with the titration method, particularly in patients receiving larger doses of opioids for background analgesia (23). This outcome is expected when one considers the level of opioid tolerance, determined by the opioid doses given for background pain.

All transmucosal fentanyl studies reported that after dose titration the most frequent effective doses were between 400 and 600 μg for patients receiving mean doses of around 120-180 mg of oral morphine equivalents. Even if they are average values that do not exclude possible variations, these data must make us reflect. It is probable that the methodologies of many studies suggesting the dose titration method have not been addressed

to the solving of this question, providing data that are difficult to interpret, given the absolute heterogeneity of the patients studied. In fact, from an overall analysis of the whole population examined in these studies, it results that a relationship with the basal dosage exists, even if within a huge individual variability (24). Many studies have confirmed the efficacy and safety of a dose at need proportional to the background dosage, i.e., the individual level of opioid tolerance(25). These doses, however, are those suggested to start treatment in patients tolerating 60 mg/day of morphine equivalents. The use of multiples in relation to higher dosages used for the basic regimen are equally effective and safe (see example in table 4).

	Doses of opioids for background analgesia	
Oral morphine equivalents	60 mg	240 mg
	Doses of opioids for BP	
EV-SC morphine	3.5-4 mg	14-16 mg
Oral oxycodone	10 mg	10 mg
Oral Morphine	10-12 mg	40 mg
OTFC	200 µg	800 µg
SLF	100 µg	400 µg
FBT	100 µg	400 µg
SLF2	133 µg	532 µg
PFNS	100 µg	400 µg
INFS	50 µg	200 µg

Table 4. Examples of proportional doses with two levels of opioid tolerance (for example 60 mg and 240 mg oral morphine equivalents, respectively, used for background analgesia.
OTFC (oral transmucosal fentanyl citrate), SLF (sublingual fentanyl), FBT (fentanyl buccal tablet), SLF2 (sublingual fentanyl), PFNS (pectin fentanyl nasal spray), INFS (intranasal spray)

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CHAPTER TEN

PAIN ASSESSMENT

Pain is a multidimensional experience that therefore requires a very accurate evaluation of the various components involved. The clinical evaluation of pain is fundamental to the defining of the therapeutic strategy. The severity of the pain is the guide for the decision making in the short or medium term regarding the modalities of intervention, more complex and aggressive attitudes being foreseen in certain emergency clinical conditions. In consideration of the subjectivity of the symptom, each assessment should start from the way in which the patient perceives the pain and from how he deals with it. Pain can be defined and described on the basis not only of the intensity, but also of the pathophysiological mechanism (nociceptive, neuropathic) for the temporal presentation characteristics (acute, persistent, intermittent). Some subjects, such as the elderly or children, may request special evaluations, such as, respectively, for cognitive impairment or due to insufficient cognitive maturation. Some factors, related to disease or individual patient characteristics, may make pain management difficult. Finally, there are some factors that may change pain expression, amplifying reported pain.

It is essential to evaluate a series of elements: the history of pain, the stage of illness, the personality characteristics of the patient (cognitive, psychological, emotional, possible drug or alcohol abuse), the intensity of pain, the interference of pain with daily activities, the interaction of pain with other physical and psychological symptoms, and the response to previous and ongoing analgesic and previous and concomitant anticancer therapies.

Even the characteristics of pain must be carefully considered: site, radiation, the factors that aggravate it, the factors that alleviate it, and the trend over time. The daily variations of pain intensity can better characterize the temporal aspect: the exacerbations of pain that overlap with peaks of greater intensity on a background pain represent a fundamental aspect, dealt with in chapter 9.

The pain symptomatology must be framed in the context of the patient's oncological disease, so it is important to know the evolution of the disease, the treatments performed, and the prognosis.

The psychological and social history is an integral part of the assessment and is necessary for the completion of a therapeutic program. A history of drug or alcohol abuse, as well as a history of chronic pain or previous use of opioids, must be considered, because these factors can complicate the treatment and are generally associated with a greater difficulty in managing therapy and in obtaining therapeutic results.

Measurement of pain

The assessment of pain intensity is of paramount importance in the cancer patient, since it represents the basis for any analgesic intervention in daily practice. In order for a measurement to be repeated, pain measurement must be valid and reliable.

The validity of a measurement refers to the appropriateness and usefulness of a measure, while reliability refers to the likelihood of deviation because of an error due to the interference of various factors, such as the patient's experience, operator, setting, or emotional factors (1).

Pain intensity can be evaluated by numerous methods. One-dimensional scales of intensity or relief can be used, as well as multidimensional questionnaires that include various aspects not exclusively related to the intensity of pain. The intensity scales are the visual analog scale (VAS), the numerical scale (NRS) (usually 0 to 10), and the verbal scale (VRS). These scales generally provide overlapping results in different clinical situations, although in certain contexts they may have choice priorities.

a) One-dimensional scales

The VAS is presented in the form of a straight line of 10 cm with verbal definitions established at the extremes, which function as a reference anchor, for example "no pain" and "maximum possible pain". Once the point on the line corresponding to the intensity of one's pain has been signaled, the score is then calculated in millimeters. A good sensitivity of VAS to changes in the intensity of cancer pain, its treatment, and a number of other measures has been demonstrated (2). In practice, the VAS can however be difficult to use for patients with low level capacity, for the elderly, or in the advanced stages of the disease.

The NRS, from 0 to 10, seems to have a common meaning even in different cultures. Words are still provided at the ends where the zero

represents the absence of pain and 10 represents the worst pain imaginable. It is finally asked to mark the number that represents the intensity of one's pain in relation to these words again. The NRS is sensitive to changes in pain intensity as a result of therapeutic changes or to evidence of an analgesic effect following short-term treatment, such as with medications used for breakthrough pain, or for repeated evaluations at longer intervals (1). A reduction of two points or a percentage change of 33% shows a good sensitivity and specificity in highlighting a clinically appreciable variation (3).

On the basis of the pain intensity's interference with the main daily functions, it was observed that a mild-bearable pain is between 0 and 4. Beyond this level the pain interferes consistently with the daily activities (moderate pain, between 5 and 6). Generally this range represents the need for a therapeutic adjustment to achieve the goal of mild pain. An intensity of pain between 7 and 10 (severe pain), on the other hand, represents a clinical imperative (4). The correlation between pain intensity and some indicators of quality of life is not always linear, since no significant differences were found between absence of pain and mild pain, nor between moderate pain and severe pain (5), and in some subjects the range of pain intensity can also be different, not always expressed in numbers. On the other hand, variations in the NRS may still offer a definite advantage for clinical decision-making in most cases.

Verbal scales (VRS) are tools that use descriptors or phrases that describe the various levels of pain intensity. Each sentence or word usually has an associated number (for example 0 = nothing, 3 = severe), with a number of descriptors included from a minimum of 4 (from 0 to 3) up to 8 levels. VRS have also showed sensitivity to therapeutic changes and a fair association with other pain intensity measures. For patients with cognitive disorders, they seem the most appropriate for simplicity and comprehensibility, for example for patients with low cultural extraction or for elderly subjects.

Some scales are characterized by the addition of verbal descriptors, "facilitators", along the lines of the VAS. The facial scales are represented by different expressions that correspond to different levels of pain, and are predominantly used in pediatrics. These scales often represent a combination of multiple elements – visual, numerical, verbal – expressed in a single scale.

Pain relief scales are often used, both as a percentage of relief and as verbal scales, and seem to be more conditioned by mood and psychological distress. Furthermore, they are not always associated with pain intensity values. The concept of pain reduction or relief is practically

useless over a long period of time, but it can be reliable over a short time, for example in studies for the acute administration of drugs lasting a few hours up to a day, as for the study of postoperative pain. The use of pain reduction rates is another fairly reliable method. The percentage of pain reduction estimated by the patient seems in fact correlated to the percentage of reduction of the NRS following an analgesic treatment (6).

b) Multidimensional scales

Pain is a multidimensional experience that involves the presence of different elements to be explored, such as the sensorial-discriminative, the motivational-affective, and the cognitive-evaluative dimensions. Therefore, measuring pain intensity may not be sufficient. There are several tools, validated and reliable, for a multidimensional evaluation of cancer pain. The best known are the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI). The BPI is based on the exploration of 7 areas of psychosocial and physical activity (scales from 0 to 10) that evaluate the intensity and the interference of pain with the usual daily activities. The intensity measurement refers to the "worst pain", the "mildest pain", and the "average pain" over the previous 24 hours along with the current pain ("just now"), expressed on the NRS. It also contains an assessment of pain relief from 0 to 100%. Its validity and reliability has also been proven in various versions in other languages.

The MPQ is a fairly complex tool, based on the use of 78 pain descriptors that comprise 3 dimensions (sensory, affective, and evaluative) and 20 subclasses, each containing 2 to 6 descriptors, in ascending order of intensity. To the sensory dimension belong 13 subclasses, to the affective 5, and to the evaluative 2. The patient is asked to choose a descriptor per subgroup, beyond the current pain intensity, on a numerical-verbal scale. Four elements can be obtained: the Present Pain Index (PPI), which expresses the intensity of pain present on the numerical-verbal scale, the number of descriptors that the patient chooses (NWC), the order in which the patient chooses the descriptors in the subclasses (PRI), and the sum of the scores attributed to the descriptors chosen by the patient (PRI). It has been translated into several languages, but the equivalence of the translated versions with the original in the English language has not been well demonstrated. The administration of this instrument is not easy. An abbreviated form has been proposed, the SF-MPQ, containing 15 descriptors, extrapolated from the sensory and affective categories, the intensity of which is assessed on a 4-point numerical-verbal scale. The score of the pain intensity is measured with both the PPI and the visual analogue. However, the Italian version did not demonstrate a superiority

over simpler scales (VAS, NRS, VRS) in the evaluation of the control of cancer pain after treatment (7). For these reasons it is mainly used as a research tool, given the complexity and time needed.

Some composite measures on quality of life combine pain intensity with interference on daily activities. The EORTC QLQ-C30 is a 30-question measure, developed to explore various dimensions of quality of life. The pain scale contains two verbal scales (intensity and interference) that are transformed into a single scale from 0 to 100. This scale showed some sensitivity to differences in outcome determined by analgesic treatments. The SF-36 bodily scale measures various dimensions of the quality of life, in which pain is examined as in the previous questionnaire.

c) Indirect measurements

The assessment given by family members, doctors, or nurses can be just as important, especially when patients are unable to express themselves directly or when it is necessary to have information at a distance. The data are controversial regarding the possible concordance between estimates made by various people.

Site of Pain

A map reproducing the human body can facilitate the evaluation of the pain sites. In practical terms, an outline assisted by possible additions, such as arrows, or colors, with respect to intensity, distribution, and irradiation of pain, is particularly useful for an immediate visualizing of the clinical picture.

Outcome measures

The Edmonton Staging System (ESS) was the first prognostic instrument proposed in the attempt to use a common language and to allow a clinical generalization of research data (8). The variables taken into account by different dimensions were the pain mechanism (visceral, bony, neuropathic, mixed), the characteristics of the pain (incident), psychological distress, previous exposure to opioids (<60 mg, 60-300 mg, >300 mg of oral morphine equivalents), tolerance (calculated as initial dose/[initial dose-final dose] x 100/day of treatment, where an increase of more than 5% per day was considered synonymous with tolerance, cognitive function, history of abuse of substances [alcoholism, drug addiction]). Three prognostic stages were created on the basis of these factors. The accuracy was subsequently examined and exposure to opioids

and cognitive function were removed, dichotomizing the categories in a more simplified system. The favorable category included visceral, somatic, non-incident pain. Nevertheless, patients prognostically disadvantaged could still achieve good pain control (9).

By using a different construct, based on the individual response to the administration of analgesics in a sequential potency border in one week, incident pain was the main negative prognostic factor, while the mechanism of pain and the dosage of opioids were not necessarily decisive, anticipating the concept of the role of individual response to analgesics, (10).

Another type of assessment concerns the measurement of the outcome. The Pain Management Index (PMI), based on the BPI, has been proposed as an index for the evaluation of the therapeutic attitude towards the intensity of pain, but it has been used subsequently to measure the efficacy of treatments in a misleading way (11). In fact it takes into account the level of pain and the potency of the analgesic drug, without considering the real use, the choice, and especially the dosage of analgesic medications. This measure can only give indications about prescriptive attitudes. According to this tool, any patient receiving strong opioids, even at inadequate doses, could be satisfied. Moreover, PMI is also a static tool. In a review of the EES, the concept of tolerance, better defined as the need to increase the dose or requiring a high escalation index, assumes a more dynamic meaning.

Opioid consumption by itself does not define the analgesic response, but the tendency to develop medium-long-term tolerance can provide useful insights into the clinical reliability of an opioid. The opioid escalation index is calculated as a percentage according to the following formula: [(x-y)/1]/days x 100, where x is the dose reached and y is the initial dose, expressed in oral morphine equivalents, or directly in mg: (x-y)/days (12).

Finally, the integration of drug use and changes in pain intensity (effective analgesic score, EAS), measured at regular intervals, for example weekly, can provide better information on clinical-therapeutic variations (13).

In a new version of the ESS, a new construct is hypothesized, according to which patients with lower clinical problems require shorter times for dosage stabilization, lower doses, and less complicated analgesic regimes, according to the concept of opioid response. The pain scores and the doses of opioids were recorded until stabilization. Only young age, neuropathic pain, and incident pain were determinants for the complexity of the treatment. Psychological stress and addiction also required higher

doses (14). However, this method is limited by the extreme therapeutic surrender of operators who prescribed only small increases in doses of opioids over particularly prolonged times to account for the time in reaching therapeutic stabilization, which is operator-dependent. The need of opioid switching is another parameter used in the evaluation of the analgesic response (15).

High pain intensity has recently been considered to be a negative prognostic factor (16). This consideration in itself may not be valid in the absolute, as it depends substantially on the time at which the patient is assessed, for example before or after an effective treatment. In fact, the intensity of pain entails a greater difficulty in treatment in terms of complexity of treatment with opioids, and time to achieve adequate analgesia, when there is a prolonged and persistent undertreatment of pain (17), probably because this situation is associated with greater psychological distress. Recently, it has been shown that in patients admitted into an acute supportive/palliative care setting, a high level of pain intensity was associated with a better outcome and patient satisfaction (18).

Factors	Grade
Incident pain	+++
Young age	++
Aberrant behavior	++
Delirium	+++
Psychological distress	+++
Neuropathic pain	++
Prolonged undertreatment	++

Table 1. Principal factors influencing pain management

Pain expression

In recent years, many factors have been found to confound, generally amplifying, pain expression. Studies have shown that patients with delirium may express higher levels of pain. In such circumstances, physicians may be mistakenly tempted to increase opioid doses, which are the possible cause of delirium. Continuous assessment of delirium should be performed to detect the deterioration of cognitive function and should alert physicians to evaluate patients for possible reversible causes of delirium, particularly in patients who are not dying (see chapter 21b).

Psychological symptoms of ESAS concur to hyper-express some symptoms and make symptom control more difficult. A clear association between anxiety and depression exists. Pain is over-expressed in patients with anxiety, while poor appetite and drowsiness have higher intensity in patients with depressed mood (19). Moreover it is well established that patients with aberrant behavior, for drugs, alcohol, or tobacco, may be resistant to opioid treatment, finally requiring higher doses of opioids and more complex pain management (20).

Minimal clinically important difference and personalized pain intensity goal

ESAS presents some limitations because of its subjectivity, as individual patients may interpret the scale, expressing their intensity with significant variations. On the other hand, the clinical response after a treatment is started is not easy to determine because the minimal clinically important difference (MCID) is not often established. The MCID is the smallest amount of change required to impact the patient's feeling of improvement or deterioration. Different methods have been variably reported to assess the MCID. They include the distribution method, based on fractionations of standard deviation or standard error, the use of anchors, for example changes of intensity categories of well-being, the magnitude of change in the patient reported outcome, or the optimal balance between sensitivity and specificity. Considering the need to evaluate the individual variations in assessing scales or numbers, it has been suggested to use the Patient's Global Impression (PGI), a validated global rating-of-change scale used to assess subjective patients' response based on the individual feeling of improvement or deterioration, after administering a particular treatment. Recently, the personalized symptom goal has been introduced as an assessment tool to tailor pain (Patients' Pain Intensity Goal, PPIG) and symptom management, providing a simple and individualized therapeutic "target" score (20). Therapeutic attempts should try to reach such threshold for an intra-patient determination of a favorable response to a treatment. The Personalized Pain Goal Response (PPGR), that is the achievement of the individual desired PPIG, is both practical and meaningful. A better characterization of the PPIG, and factors associated with the PPGR and PGI, as perceived by patients, would help clinicians to personalize pain management and to evaluate meaningful changes. This is even more important in a palliative care unit, which is the setting where pain and symptom management can be more rapid and effective, because daily assessment, expertise, and timely

therapeutic changes may provide a better control of pain and symptoms in a short period. In a recent study (21), we found a mean PPIG of 1.33. To perceive a minimal clinically important difference (MCID), a mean decrease in pain intensity of -2.09 was required on the PPIG. A better improvement and a much better improvement corresponded to a mean change of -3.41 and -4.59 points, respectively. Patients perceived a MCID (little worse) with a mean increase in pain intensity of 0.25, and they perceived a "worse" with a mean increase of 2.33 points. Higher pain intensity at baseline and lower pain intensity after comprehensive symptom management were independently related to the PGI. 30% of patients achieved the PPGR. The PPGR was associated with higher PPIG at baseline and after treatment, and inversely associated both to pain intensity at baseline and after treatment and to Karnofsky level. Patients with high pain intensity at baseline achieved a favorable PGI, even when the PPIG was not achieved by the PPGR.

Thus, PPIG, PPGR, and PGI seem to be relevant for evaluating the effects of a comprehensive management of pain, assisting in the decision-making process according to patients' expectations. Some factors may be implicated in determining the individual target and the clinical response.

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CHAPTER ELEVEN

PHARMACOLOGICAL TREATMENT: GENERAL CONSIDERATIONS

In 1986 the World Health Organization (WHO) published guidelines for the treatment of cancer pain based on a three-step scale according to a sequence of drugs with increasing potency (1). The WHO analgesic scale suggested the use of non-opioid drugs for mild-moderate pain associated with possible adjuvant drugs. If the pain was not controlled, the so - called weak opioids were suggested, associated or not with adjuvant drugs, while if pain persisted or appeared severe, the use of strong opioids, associated or not to adjuvants, was indicated. The main purpose was the legitimization of the use of strong opioids, which arose from the remarkable cultural and institutional resistance that prevented their prescription, based on unfounded fears regarding side effects, dependence, abuse, or illicit use. Its application has allowed formidable results to be obtained in clinical terms, allowing the provision of adequate pain control to the majority of patients treated according to these indications, using simple and inexpensive means, and therefore diffusible even in poor countries.

First step

The first step of the WHO ladder proposes the use of non-opioid drugs, associated or not with adjuvants. The studies in this regard have been re-evaluated by many meta-analyses, which have underlined many methodological problems concerning the heterogeneity of the study designs, the parameters evaluated, and the results taken into consideration. The prolonged use of non-opioids, mainly anti-inflammatory, is particularly risky, particularly in the elderly and in dehydrated patients. The continuation of anti-inflammatory drugs after opioid therapy on the second and third steps is potentially suggested by the WHO guidelines, leaving the appearance of side effects as a criterion for their discontinuation. However, the side effects are quite ambiguous, often

insidious. The greatest risks are represented by potential organ injuries, in some cases dramatic or fatal, rather than reversible side effects with drug discontinuation. The conclusions of some recent studies propose a different approach: opioids are administered in the first instance and then anti-inflammatory drugs are added under certain conditions to the limits of opioid toxicity or in cases of a particular favorable therapeutic response able to curb the clinical demands of opioids or reduce the dosage (2). A position of this kind reconciles different clinical evaluations and habits, such as those of the US, very reluctant regarding the use of anti-inflammatory drugs, and those of Europe, particularly generous in the use of these drugs (3). Patients could then start opioid therapy and use non-opioids in selected cases that respond very effectively to such drugs to allow an agile use of opioids to increase doses, thus preventing possible toxicity. The efficacy of anti-inflammatory drugs applying only in certain syndromes, such as bone metastases, is not supported by data that demonstrate an independent efficacy, at least in the predominantly nociceptive syndromes (4).

Second step

The role of so-called weak opioids in the treatment of cancer pain has been questioned for years, as if it could be skipped to proceed directly to the third step, which involves the use of strong opioids. In fact, some drugs of the second step, such as codeine, are actually pro-drugs whose activity is dependent on morphine transformation, which is traditionally considered a strong opioid (see chapters 14 and 16).

On the other hand, some studies have evaluated the immediate use of strong opioids in opioid-naïve patients, skipping the second step. While the use of so-called strong opioids at traditional doses of 60 mg of oral morphine equivalents is to be ruled out, being as it would induce high risks of side effects in naive patients, very low doses subsequently titrated according to need result in a step aimed at understanding a difficult management of containers (the steps), which in reality can include many drugs, the dosage of which can be modulated according to the circumstances. Therefore the target is no longer the step to use, but the dosage of a substance for a given intensity of pain. Morphine administered in initial doses of about 15-30 mg, divided during the day, allows an adequate titration, particularly safe, with a high tolerability index particularly in the elderly patient, in a range of pain intensity generally reserved for weak opioids. Therefore, an early introduction of morphine, but at a dose proportional to the entity of the problem, does not involve an

exaggerated risk of increasing the subsequent doses (5). This aspect will be better detailed in the chapter reserved for opioid titration (chapter 19a).

Third step

Morphine is considered the standard drug for the treatment of severe pain for a series of considerations related to the wide experience in use, the extreme availability of numerous formulations in all countries, and the low cost of therapy. However, there is no concrete evidence that morphine is the drug of choice in terms of clinical superiority over other opioids. Individualization of therapy should be emphasized to minimize side effects and improve the analgesic response. A certain percentage of patients (about 20%) do not respond effectively and require other pharmacological solutions (6). A clear individual difference in terms of response to different opioids is becoming increasingly evident. Patients who are poorly responsive to a drug can better tolerate a second opioid. An opioid substitution may result in an improvement of the analgesia-side effects balance in most patients (chapter 19d) who have an unfavorable opioid response, generally at lower doses than those expected, considering a complete cross-tolerance between the two drugs. The drugs traditionally considered "alternative" to morphine and commonly used are hydromorphone, oxycodone, hydrocodone, and methadone, as well as transdermal drugs, such as fentanyl and buprenorphine, and tapentadol.

Other studies have shown that even the administration of slow-release drugs, if assisted by drugs when needed, can produce an efficient analgesia in a short time during the induction of analgesia (7), contradicting some assumptions that lead to a preferential choice of immediate release morphine to facilitate opioid-induction, reserving controlled release morphine for the maintenance phase (8). Another study confirmed the usefulness of doubling the immediate overnight dose of morphine, compared to the dose administered at midnight. The advantage is still reasonably more evident in clinical practice where it will be carefully avoided to awaken a patient to administer a drug at 2 a.m. (chapter 16).

Therefore the clinical conditions and the different needs will dictate the order of priority in the choice of an opioid and the route of administration. This involves the need to know deeply the characteristics of these drugs, described in detail in chapter 16, and to deepen clinical confidence of when it is necessary to use them in the first place. The relationship between efficacy, convenience of administration, patient preference, degree of satisfaction, and costs should be examined in appropriate studies.

Adjuvants

Adjuvants include a large group of drugs with different pharmacological characteristics and are present along all the steps of the WHO guidelines in a fairly generic manner, leaving the choice and the opportunity of use to clinicians. These drugs are used to improve the analgesia of non-opioids and opioids, but above all to mitigate the side effects of higher doses of opioids.

However, despite the frequent use of these drugs, there is little evidence to support the efficacy and tolerability of these treatments in cancer patients. Antidepressants, anticonvulsants, and corticosteroids are the most used drugs of the first category, while antiemetic and laxatives are the most commonly used for the second class of drugs. The characteristics of these drugs and their clinical efficacy will be considered in specific chapters. Despite the absence of relevant evidence, decades of experience suggest that the role of these drugs is crucial during a comprehensive management of cancer pain. In some cases, for example in long-term or disease-free patients, but with painful treatment outcomes, they may be first choice drugs to replace opioids.

Emerging issues

In the years of evidence-based medicine, the three step analgesic scale has been targeted due to the lack of robustness of scientific data supporting these data. All the studies carried out on the analgesic scale proposed by the WHO in fact had undoubted methodological limitations, such as the type of assessment and the circumstances in which they were performed, the low value of the samples examined, retrospective analysis, the high proportion of patients leaving studies, inadequate reassessment over time, the absence of comparative elements of pain intensity levels or comparisons between different methodologies or different drugs (9).

Some elements of weakness in these guidelines have been taken up in recent years to corroborate or, on the contrary, to correct traditional indications. In particular, the use of the first and second steps has been questioned in recent years, as well as the possible differences between strong opioids or routes of administration in particular conditions where absolute individualization of treatment is required, or the use of adjuvants. In some cases the non-application of the guidelines has been due to the lack of availability of drugs in some countries of the world. The European Association for Palliative Care examined in particular the use of morphine

and other opioids according to a principle based on the scientific evidence of some statements (10) (table 1).

1. The drugs of the second step, codeine or tramadol can be used in patients with mild-moderate pain. Alternatively, low doses of strong opioids. Weak recommendation.
2. For severe moderate pain strong opioids are equally effective. Weak recommendation.
3. Opioids of immediate and slow release of morphine, oxycodone, and hydromorphone may be used for titration of the effective dosage, if immediate-release preparation is available. Weak recommendation.
4. Transdermal opioids, fentanyl, and buprenorphine, may be used as an alternative to oral opioids and are preferable in some circumstances, such as in the absence of the ability to swallow. Weak recommendation.
5. Methadone has a complex pharmacokinetic profile and may be used in severe moderate pain, by experienced personnel. Weak recommendation.
6. A substitution of the opioid in the presence of an unfavorable balance between analgesia and side effects may be effective. Weak recommendation.
7. Conversion ratios between opioids are quite specific for patients with good pain control. In other cases, experience suggests starting with lower doses of equianalgesic conversion ratios and subsequently titrating according to the clinical response. Weak recommendation.
8. The subcutaneous route is effective and simple and should be the first choice alternative to the oral or transdermal route. Strong recommendation.
9. The intravenous route should be considered when the subcutaneous route is contraindicated and for rapid dose titration. The conversion ratio between oral and parenteral is 3-2: 1. Although the rectal route can be effective, it is not acceptable to most patients. Weak recommendation.

Table 1. Main recommendations on the use of opioids

It is quite evident that many of these recommendations are based on clinical experience rather than on concrete data, underlining the need to consolidate in a scientific way many clichés generated by a large amount of experience in the field.

Initial steps

The initial steps are of fundamental importance and make a permanent impression on the subsequent treatment. These steps follow fundamental points to allow therapeutic decisions to be made.

a) Detailed clinical history to recognize the causes and mechanisms that underlie pain.

b) Pain intensity is a fundamental guide for the beginning of an analgesic treatment. The temporal variations of pain during the day will have to be specifically identified (see chapter 9). Re-evaluation of pain intensity at regular intervals.

c) Analgesic history: the variability in opioid response is well documented. Some patients may surprisingly respond with a second opioid, after the first one was ineffective or had produced unacceptable side effects limiting eventual dose increases. The reasons for this variability will be explained in the following chapters (chapter 19c). This phenomenon will influence the selection of drugs apparently belonging to the same class. Naive patients will require lower doses than patients who have already developed tolerance for opioid analgesic effects. In some cases, however, more intensive treatment that includes powerful drugs with faster doses from the beginning is required (see chapter 19a), especially when treatment has been inadequate for a long time. High starting doses should be evaluated carefully.

d) Pre-existing conditions: certain comorbid situations may influence the choice of an opioid. Renal impairment of a certain degree precludes the use of morphine or at least dictates a more complex use in terms of predictability of effects and risks. The presence of vomiting or the unavailability of the oral route, or the presence of important intestinal resections that limit the absorption of oral medications, favors the use of independent, transdermal, sublingual, or parenteral pathways.

e) Evaluation of the psychological profile.

f) All-inclusive evaluation of symptoms due to disease or opioid administration.

g) Exploration of realistic goals related to the patient's pain intensity
h) The drugs are administered at fixed times, guaranteeing also medications as needed for breakthrough pain. The drugs are administered orally if patients are able to swallow; otherwise the preferential routes are the transdermal, subcutaneous, or intravenous.
i) Weighted use of adjuvants.
j) Each therapeutic plan will be individualized and re-evaluated frequently.
k) General information on the treatment of cancer pain and reassurance about the benefits and possible side effects
l) Information on local resources (home care, hospice, oncology hospitals)

Table 2. Mandatory steps for pain management

Barriers to effective treatment

Unfortunately, cancer pain continues to be ineffectively treated, despite the presence of pharmacological means in the third century even more efficient than those available when the first guidelines were drafted. The use of opioids is inadequate compared to the probable requirements for regulations that limit access to medicines, due to lack of economic resources and negative perceptions by professionals, family members, paents, and the mass media about the use of these drugs

The legal and bureaucratic aspects have for years been a considerable burden for an appropriate prescription of opioids, often providing an alibi for many doctors. Therefore the poor use of opioids is linked exclusively to cultural matters.

The education by doctors and nurses on cancer pain and its treatment is particularly inadequate. The know-how remains inadequate with regard to side effects, familiarity with opioid pharmacology, and a series of fears and beliefs regarding certain aspects such as addiction, tolerance, and respiratory depression. These barriers persist and represent a strong obstacle to the proper use of these drugs.

Even family members can put up barriers to the proper use of opioids, mainly due to a certain reluctance also linked to fallacious information on these drugs. Elderly people and children, for example, represent a special category which, due to a number of factors concerning comorbidity, fragility, pharmacokinetics, and pharmacodynamics, are often underestimated (11, 12). In various surveys carried out in cancer institutions, a worrying lack of the basic principles of cancer pain treatment has emerged, with peaks elevating undertreatment (13). Pain barriers are now considered a factor limiting adequate management and are regularly assessed (14). In the last few decades, the consumption of opioid analgesics in many countries, particularly the US, has dramatically increased. This rise has been paralleled by a proportional number of opioid-related deaths. The recent opioid crisis, substantially due to an inappropriate use of opioids and poor monitoring, has had a tremendous impact on the media, limiting the proper use of opioids in cancer patients. Pain physicians should provide multidimensional management as the paradigm for responsible opioid treatment. Interventions should focus on preventing new cases of opioid addiction, identifying early cases of opioid addiction, and ensuring access to effective addiction treatment. Many activities have been suggested to face the opioid epidemic, but clinicians should find a fine balance that meets the patient's need for pain relief while minimizing the chance for abuse (15).

Conclusions

The method suggested by the WHO remains of fundamental importance for the great cultural turning point that has provided universal and repeatable means everywhere at low cost. The absence of scientific evidence is offset by the clinical results reported at various latitudes on huge samples of patients. Therefore the WHO strategy can represent a pathway for intervention for a first line doctor. On the contrary, in the specialist setting, in most cases an additional interpretative effort should be made to individualize the treatment of pain with the available drugs, widening the effectiveness percentages tending to 100%, objective achievable with an accurate evaluation and a personalized treatment.

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CHAPTER TWELVE

NON OPIOID ANALGESICS

Corticosteroides

The term corticosteroid drugs emphasizes the characteristics of these drugs that can reproduce the biological actions of hormones produced by the adrenal cortex. The adrenal cortex, in addition to producing steroids with androgenic or estrogenic activity, is able to synthesize cholesterol derivatives that act mainly on the metabolism of carbohydrates (glucocorticoids) or modifying the hydro-saline balance (mineralcorticoids). All the molecules of this class behave in a substantially overlapping manner with respect to the glucose metabolism, while they possess substantial differences in carrying out a sodium-retentive and anti-inflammatory activity. Dexamethasone and betamethasone have a high anti-inflammatory activity and also a minimal sodium-retentive activity, compared to other drugs of the same category. Differing anti-inflammatory activities involve different dosage choices depending on the drug used and the indication. Apart from hydrocortisone, which has a relatively short half-life (12-18 hours), almost all the other drugs have a rather prolonged half-life (over 24 hours), which also accounts for the effect being sustained over time, allowing a daily administration.

	Anti-inflammatory activity	
Mineral-corticoid activity		
Betamethasone	25	0
Dexamethasone	25	0
Methylprednisolone	5	0.5
Prednisone	4	0.8
Prednisolone	4	0.8
Triamcinolone	0.5	5

Table 1. Anti-inflammatory and sodium-retentive activity of the main steroidal anti-inflammatory drugs. Potency related to cortisol (anti-inflammatory) and hydrocortisone (mineral-corticoid).

- Mechanisms of action

Corticosteroids act by inducing gene transcription for the synthesis or the inhibition of some protein substances, mainly enzymes. The binding to the receptors on which the same endogenous steroids have an activity occurs at the cytoplasmic level, where an active complex is formed that is addressed to the nucleus, interacting with some DNA sequences that regulate the target genes. The immunosuppressive action recognizes typical molecular bases: the inhibition of the transcription of genes that code cytokine synthesis and the synthesis of their receptors, the interaction with transcription factors activated by cytokines, the inhibition of the transcription of the gene encoding cyclooxygenase 2, the phospholipase A2, the inducible form of the NO synthase, the adhesion molecules, which favor the transmigration of the inflammatory cells through the endothelium, and finally the synthesis of the receptors of the substance P and of the beta-adrenergic bronchial receptors (1). For these characteristics, the time taken to observe the effects of steroid anti-inflammatory drugs is significantly longer than that of non-steroidal compounds. Similarly, the times for the disappearance of an effect, for example hyperglycemia, are equally prolonged.

-Tolerability

Dexamethasone is probably the most convenient drug due to a lower sodium-retentive activity. Corticosteroid administration in cancer patients is often associated with oral candidiasis as a consequence of the immunosuppressive effect. In some cases prolonged treatments with corticosteroids are responsible for the appearance of pseudorheumatism, which appears especially during the dose reduction phase. Another complication that is expressed with a pain syndrome is represented by aseptic femoral humeral necrosis, which may appear even after short treatments. While in the short term the euphoric and perishing effects are well known, central effects and changes in behavior and mood have also been described, especially in children where they may lead to depressive episodes, attention deficit, and hyperkinesia (2).

The frequency and severity of side effects increase proportionally to the duration of treatment and the dosages used. Therefore, prolonged treatments must be reserved for cases of imperative necessity, which however are frequent in rheumatological practice and in cancer patients. The development of osteoporosis is very frequent (30-50%) in patients treated chronically with steroidal anti-inflammatory drugs, and is the

consequence of a series of negative effects on calcium metabolism: inhibition of intestinal absorption, indirect activation of osteoclast activity, and direct inhibition of osteoblast activity. The gastrolesive activity is a well-known and often feared effect during treatment with corticosteroids, but the appearance of important gastro-duodenal lesions is actually a rather rare event. However, the risk increases significantly during the co-administration of other drugs with a higher gastric activity, such as non-steroidal anti-inflammatory drugs, which is also not rare in clinical practice.

The abrupt suspension of the treatment is insidiously expressed with the appearance of quite unspecific symptoms such as fever, asthenia, and widespread pain (arthralgias, myalgias). Compared to such phenomena, however important, the hormonal effects of counter-inhibition exercised by corticosteroids administered for prolonged periods on the hypothalamic-pituitary-adrenal axis, with consequent zeroing of the production of endogenous cortisol, can lead to a sudden absence of endogenous substances with mineral corticoid activity. The recovery of an adequate hormonal activity occurs in some weeks, due to the characteristic transcriptional activity of these substances, whose effect is therefore prolonged. A gradual suspension with progressively decreasing doses reduces the risk of acute adrenal insufficiency. The abrupt suspension is able to produce important psychotic phenomena (3), reproducing a symptom very similar to that produced by the prolonged administration of corticosteroids.

-Clinical use

Corticosteroids represent a group of drugs frequently used for symptomatic purposes in various clinical conditions in the cancer patient, for example for the compressions caused by large neoplastic masses in demarcated areas, or in the presence of a perineoplastic edema with compression of nearby areas, particularly vascular, capsular, and ductal (4). Despite the frequent use of these drugs, the scientific evidence on the role of adjuvant analgesic is scarce (5-7).

The dosages used, resulting exclusively from clinical experience, are quite variable, from 4-8 mg of dexametazone, the most used corticosteroid, in nerve compression or in bone metastases, up to 50-100 mg prescribed in the presence of cerebral compression headache (8). The choice resides on higher doses for short periods, rather than for the administration of repeated lower doses over a prolonged period of time, which is associated with the development of oropharyngeal candidiasis. In

reality the indications for the use of corticosteroids in cancer are many and such that it is difficult to discern a clear benefit for a specific indication (9).

Specific uses
- Hypercalcemia
- Medullary compression paraplegia
- Airway obstruction dyspnea, lymphangitis, vena cava syndrome
- In association with chemotherapy and radiotherapy
- Tenesmus, rectal secretions
- Intestinal obstruction
- Vomiting
Analgesic action
- Intracranial hypertension
- Hepatomegaly
- Pelvic and abdominal masses with nerve compression
- Tumors of the head and neck
- Lymphedema
- Adjuvant in peripheral blocks with local anesthetics
General effects
- Improvement of appetite and sense of well-being
- Temperature reduction

Table 2. Indications for the use of corticosteroids

Regarding the treatment of cancer pain, corticosteroids, although not exercising any direct analgesic activity, are mainly used in the presence of bone metastases or infiltration-compression of the nerve structures, conditions where a reduction in the edemigenic part can significantly reduce the painful source, although there are no specific studies that have ever been able to demonstrate a clear benefit (10, 11).

Corticosteroids are often used for nausea and vomiting, particularly when these symptoms are associated with cerebral hypertension. Headache from intracranial hypertension and spinal compression is a primary indication (chapters 25 b and 25g) and requires high doses. Moreover they could have positive effects in the states of intestinal sub-obstruction (chapter 22d) for the reduction of the edemigenic component, responsible for a stupor of the intestinal nervous plexus. This effect can be extended to other symptoms, such as a sense of well-being, appetite loss, dyspnea, or

clinical conditions, such as hypercalcemia or paraneoplastic hyperthermia. These benefits, limited in time, are well known in the advanced patient (7). The general effects on the feeling of well-being, activity, mood and appetite, and nausea and vomiting are frequently observable, even if temporary. The importance of long-term side effects has never been well established. In patients with limited expectation, corticosteroids do not appear to produce significant problems (11).

Non-steroidal anti-inflammatory drugs (NSAIDS)

NSAIDs form a very heterogeneous group, even though they have similar general effects: anti-inflammatory, analgesic, and antipyretic.

Drug	Dose (mg)	Duration	Half-life	Toxicity
Acetylsalicylic acid	600	4-6 h	3-12 h	++
Diclofenac	100	8-12 h	1.5 h	+
Naproxen	550	12 h	12 h	+
Ketoprofen	200	6-8 h	1.5 h	++
Indomethacin	75	6-12 h	6 h	+++
Ibuprofen	200	8 h	2.5 h	+
Ketorolac	20	8 h	4-7 h	++

Table 3. Comparative pharmacology of traditional NSAIDs

-Mechanisms of action

All the effects of NSAIDs are strictly linked to the inhibition of cyclooxygenase enzymatic activity (COX) and to the reduced production of prostaglandins and thromboxane. Prostaglandins (PGs) are imputed to favor the onset and maintenance of a condition of hyperexcitability of nociceptors and spinal neurons (see chapter 7). NSAIDs are able to exercise other biological actions that affect both some cells of the immune system and single mediators of inflammation, important for the appearance of the anti-inflammatory and analgesic effects (12). Substantially, they inhibit the chemotaxis of monocytes and granulocytes, the release of histamine, the production of superoxide anion and metal-protease, and the formation of leukotrienes and nitric oxide.

COX-1 selective	balanced	COX-2 selective
Ketoprofen	Ibuprofen	coxibs
Ketorolac	Diclofenac	
Indomethacin	Naproxen	
Acetylsalicylic acid	Nimesulide	

Table 4. NSAID selectivity characteristics for COX isomers

From the pharmacokinetic point of view these agents have similar characteristics. They are generally well absorbed through the gastrointestinal system, have a limited distribution volume due to their high protein binding, and are metabolized in the liver with a minimal renal excretion. The clearance values are generally low and extremely sensitive to changes in plasma protein binding. Some of these drugs also have a strong penetration into the central nervous system, due to their characteristics of liposolubility, where they exert their anti-prostaglandinic action (13).

	Estimated risk
Ketorolac	24
Indomethacin	10
Ketoprofen	10
Acetylsalicylic acid	8
Diclofenac	3
Ibuprofen	3
Nimesulide	3
Rofecoxib	7
Paracetamol	1

Table 5. Risk of bleeding of the upper digestive tract of NSAIDs with respect to paracetamol.

-Tolerability

Acetylsalicylic acid (ASA) has been the reference drug in terms of both anti-inflammatory effect and toxicity and is the only active substance that irreversibly inhibits the activity of platelet COX, unlike other substances of the same category. The selective COX-2 inhibitors have been proposed as drugs able to guarantee the same therapeutic efficacy of

first generation NSAIDs, potentially without inducing the same undesirable effects. It has been widely demonstrated that there are no substantial differences between selective and non-selective compounds as regards the renal function. Regarding the effects on the aggregation process, it should be noted that the platelets are not able to synthesize COX-2. It follows that the synthesis of thromboxane B2 and, therefore, the aggregation of these elements depends exclusively on the activity of COX-1. Therefore, drugs that exert their therapeutic action without causing a marked inhibition of COX-1 do not modify bleeding time in a clinically relevant manner. In patients receiving NSAIDs chronically, the annual incidence of serious events such as ulcers, bleeding, and perforations is estimated to be between 1% and 4%, while erosions that are identifiable by endoscopic examination occur in 35-60% of cases. Therefore, NSAID damage determines very high annual costs, particularly in patients with risk factors. The existence of only one factor involves a risk of 2% and that of all factors a risk of 18% (14). Bleeding episodes of the upper tract are dependent on the type of NSAIDs, but are independent of the selectivity of action on COX-2. Regardless of the type of drug, the use of high dosages results in a significant increase in the risk of bleeding. Overall, the available data suggest that selective COX-2 inhibitors may reduce but certainly do not eliminate the risk of serious complications such as ulcers, bleeding, and perforation. Age is undoubtedly a factor of great importance. Patients with the highest risk of experiencing severe NSAID gastrointestinal damage are thought to be older and to have a history of peptic ulcer disease. The cancer patient population has many of the risks, especially taking into account the possible prolonged administration (table 6).

Type of medication
Dose of drug
Age over 65 years
Concomitant use of drugs such as anti-aggregants, anticoagulants, and corticosteroids
Prevalent peptic ulcers (especially if very recent)
A history of bleeding or gastroduodenal perforations
Smoking

Table 6: Major risk factors for NSAID gastroduodenal toxicity.

The identification of the various risk factors is of primary importance for deciding in which subjects it is appropriate to associate a

gastroprotective agent with NSAIDs. Proton pump inhibitors are the most effective molecules (15).

It has also been observed that a prolonged and exclusive inhibition of the enzymatic activity of COX-2 is associated with a greater risk of cardiovascular accidents on a thromboembolic basis, correlated with a persistent reduction of prostacyclin production (the synthesis of which depends on the COX-2 activity) unbalanced by a reduced formation of thromboxane A2 (the synthesis of which depends on the activity of COX-1) (16).

-Clinical use

Traditionally, this group of drugs is used for moderate pain as a first approach and subsequently in subsequent steps in association with opioids, when they lose their analgesic efficacy. There are not many studies of evidence in favor of this rather heterogeneous class of drugs (17). The most important problem of these drugs is the irregular dose-response curve. An increase in dosage generally does not produce a corresponding analgesic effect but increases the risks of side effects. In some cases it is also necessary to suspend the treatment due to the occurrence of side effects, in a population prevalently represented by elderly patients, notoriously more at risk for gastric and renal lesions (17). The use of NSAIDs, both initially and subsequently on the analgesic scale, has never been supported by clear clinical evidence. In fact, this data is scarcely evaluable in the long term, when the analgesic effect of these drugs is however dwarfed by that of the opioids typically used in increasing doses. Furthermore, the need to administer gastro-protectors in a broad range of the population at risk imposes some caution according to a pharmaceutical-economic consideration (18). However, there are patients particularly sensitive to NSAIDs, and their use is justified in well selected cases due to the undoubted analgesic advantage. Therefore, NSAIDs could be used as adjuvants in patients who are already receiving opioids and who are particularly sensitive to their administration to the point that they allow a reduction in the tendency to increase the doses of opioids and, therefore, a lowering in the risk of opioid induced adverse effects (19). This approach, which substantially modifies the traditional approach, makes it possible to use NSAIDs more effectively and clearly, in a small group of patients who gain a clear benefit and for a shorter period of time, compared to an early administration, and potentially prolonged ad libitum, as traditionally suggested (see chapter 11). This clinical advantage also

translates into a significant reduction in the costs of therapy generally associated with the use of opioids.

Paracetamol

Paracetamol is not considered an NSAID. It has no antiplatelet activity and its anti-inflammatory activity is very weak. This anti-inflammatory action is believed to be attributable to a weak inhibition of the prostaglandin synthesis pathway, mostly dependent on COX-2. Other than the inhibition of COX-2, it appears that there is a third isoform of cyclo-oxygenase expressed in the brain (COX-3) that could be the preferred target of paracetamol and other antipyretics. The inhibition of this enzyme, which has been shown to be a molecular variant of COX-1, could account for some of the central analgesic and antipyretic effects mediated by paracetamol (20). Paracetamol can be administered through different routes and has a high bioavailability, which does not undergo major changes, except in the presence of liver disease. In fact, at the level of the liver, the molecule is transformed into a metabolite that has proved toxic to the liver tissue. The analgesic effect appears promptly after oral administration and the half-life of the drug is 1-4 hours. The maximum recommended dose is 3 grams per day and the single dose should not exceed one gram (21).

A risk related to its use is represented by its presence in different drug combination preparations as this often leads to overdose. Paracetamol is metabolized by cytochrome enzymes that convert paracetamol into N-acetylbenzoquinoneimine, a very reactive and toxic compound for liver cells. Currently, paracetamol is the least nephrotoxic drug among those used for pain and is considered for this reason as the first choice in subjects with renal insufficiency who cannot use the traditional NSAIDs. Data in cancer pain are quite scarce and the analgesic effect has never been adequately evaluated (22).

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CHAPTER THIRTEEN

ANALGESIC ADJUVANTS

Neuropathic pain is characterized by a considerable variability in the mechanism of the lesion and in the clinical presentation, even in the presence of similar basic diseases. This consideration is even more pronounced in cancer pain, where there is a mutability in the clinical picture in relation to the progression of the disease or to some therapeutic interventions. Ideally, the development of an effective treatment algorithm"? should be based on the comparison of available drugs, both for analgesia and tolerability. Unfortunately, comparison studies in cancer pain are rather poor and generally data from studies carried out on patients with non-cancer neuropathic pain are adapted to patients with cancer pain (1).

Neuropathic pain has been treated in a variety of ways, often without guiding protocols. In recent years, evidence-based medicine has revolutionized many traditional aspects of the use of certain drugs, previously often based on personal experience and not fully substantiated by scientific data of a given depth. Although the absence of evidence cannot be considered the absence of an efficacy of a given treatment, scientific demonstration based predominantly on controlled and randomized studies allows us to obtain a more objective evaluation. In recent years, studies have multiplied with more refined and above all reliable methods for the number and homogeneity of patients. Even these studies can present flaws in terms of quality. Therefore, additional means of evaluating not only statistics but above all the quality of published studies are layers. Meta-analytical revisions, evaluating the data of homologous studies, have allowed the reinforcement of the statistical meaning of several works put together numerically, but which can differ from the qualitative and proactive point of view, sometimes providing conflicting data.

In most of the critical studies that analyze the literature, numerical parameters are often reported, which allow the identification of the efficacy of a treatment compared to a control, commonly the administration of placebo, using net and dichotomous criteria. For

example, a response is considered effective when an active treatment produces a symptom reduction of at least 50%. The number needed to treat (NNT) is the expected number of patients one would need to treat to achieve a single occurrence of a specified good outcome (e.g., 50% reduction in pain intensity) in comparison to no (or placebo) treatment. The formula to get this number is: NNT = 1 / (n effective treated / total n treated) - (n effective placebo / n total placebo). A number between 2 and 3 corresponds to a treatment with a fairly effective drug, while a high number means that a large number of patients must be treated to have a responsive one, compared to a placebo treatment. For side effects, the use of the number needed to harm (NNH) is invaluable, which should mutually correspond to a high number to evaluate a drug as well tolerated, i.e., many patients are required to observe a side effect.

These indicative values will be considered frequently in this chapter, when reported in the literature, in order to make a rapid assessment of the effectiveness of a drug in a given clinical condition. However, it should be stressed that in pain management, most of these drugs are often used clinically, with a combination of drugs to additively or synergistically improve the overall treatment performance. Unfortunately, the scientific reliability of the associations used in clinical practice has never been established in appropriate clinical studies, which are however very complex to perform. Thus, the optimization of drug combinations has been left to individual experience.

Numerous studies and consolidated experience have shown that the classification and treatment of pain on the basis of anatomical aspects and primary disease are of limited value. These observations have given rise to a fascinating question concerning the mechanistic approach in the treatment of neuropathic pain. The possible stratification of drugs against neuropathic pain according to mechanism is presented in figure 1.

Ideally, by identifying the mechanism through which the nerve injury is active in each subject, it should be possible to select a drug with the capacity to modulate these mechanisms (2). Unfortunately, despite the progress and the improvement of knowledge on pain mechanisms thanks to experimental animal models, it is not currently possible to stratify the treatment according to a mechanistic approach. In fact, from a practical point of view it is not clear whether this produces a better result from the clinical point of view. Many factors contribute to a limiting of the meaningfulness of this approach. There is no diagnostic test that confirms the presence of a nerve injury (defined, probable, possible, unlikely) or quantifies an entirely subjective perception. Moreover, unlike other sensory systems, the pain system is not static and dynamically changes in

an unpredictable and completely individual manner. Signs and symptoms can in fact vary over time during the course of a disease. Finally there is a clear individual difference in the response to drugs. In general, a pharmacological response is obtained in about one third of patients regardless of the location and type of disease. Lacking the possibility of ascertaining with reasonable certainty the presence of a fairly elusive clinical state, it is also difficult to establish a relationship between mechanisms, signs and symptoms, and pharmacological response (3). This assumption is confirmed by the absence of a relationship between the response to drugs deemed sufficiently effective in neuropathic pain and the probable presence or absence of a nerve injury (4), as with the indiscriminate efficacy in terms of the NNT, indistinguishable for syndromes completely different.

General considerations on the treatment of neuropathic pain

The quality of currently available evidence on the effectiveness of adjuvants, principally those used for neuropathic cancer pain, is low. Thus, the treatment should be tailored to the patient's personal characteristics and preference (5).

Algorithms and recommendations on the pharmacological treatment of neuropathic pain have been developed in recent years. There is not enough data to establish an order of preference in terms of greater analgesic efficacy, nor for other important variables, such as the potential to cause side effects and interactions with other drugs, or the effects regarding possible comorbidities, such as anxiety, insomnia and depression, costs, risks of abuse, and disproportionate doses. Individual variability in response to the drugs in question is substantial and unpredictable. Furthermore, the combination of drugs is the norm in clinical practice. The potential advantages, found for example by the association gabapentin-morphine with respect to single drugs, must however be weighed against the possible occurrence of additive side effects (6). Indeed, no difference in efficacy or side effects between pregabalin combined to duloxetine at moderate dosages (300 mg pregabalin, 60 mg duloxetine daily) and monotherapy at high dosages (600 mg pregabalin, 120 mg duloxetine daily) in patients not responsive to monotherapy at moderate dosages was found (7).

The first-line drugs include tricyclic antidepressants and α2-δ calcium channel ligands (gabapentinoids). Opioids, contrary to that indicated in a previous publication, have been relegated to the second line in relation to

the risk of higher abuse (8). In fact, the problem in cancer pain is so different that opioids are routinely administered in the first instance, considering that a pioneering mechanistic approach, based on the priority use of antiepileptics or antidepressants in cancer pain with a neuropathic prevalence, was unsuccessful. In fact all the few patients left in the study inevitably needed the use of opioids (9). Given that basal analgesia in most cases of moderate-severe pain is based on an opioid, it is quite obvious that all the drugs in question will be administered in addition as potentially in clinical conditions where neuropathic phenomena are particularly evident (10).

In cancer pain there are few studies on tricyclic antidepressants and gabapentinoids to mention (11). In a cross-over study, short-lived patients with neuropathic pain treated with morphine having uncontrolled pain, received amitriptyline in increasing doses of 25-50 mg in one week compared to placebo. There were no substantial benefits in terms of morphine dosage and intensity of background pain, except for with the worst pain. However, side effects increased markedly (11), confirming the lack of clinical advantage in relation to the preponderance and enhancement of side effects in patients receiving numerous drugs including opioids. Gabapentin has shown some efficacy, in addition to opioid therapy in various experiences, demonstrating greater handiness in the context of cancer disease both in controlled studies (12, 13) and in observational studies (14), in which, however, the effect seemed to be decreasing over time. The main advantage is the absence of interactions with the multitude of drugs used during all stages of the disease. A recent meta-analysis showed that combining opioids with gabapentinoids did not significantly improve analgesia in patients with cancer-related pain compared with opioid monotherapy. Due to the heterogeneity of patient samples, benefits in patients with definite neuropathic cancer pain cannot be excluded. Clinicians should balance the small likelihood of benefit in patients with cancer-related cancer pain against the increased risk of adverse effects of combination therapy (15).

Different considerations should be made in long-term survivors, where the use of these drugs has priority over opioids, as in the case of non-cancer pain. Anticonvulsants and antidepressants are particularly used in post-surgical or post-radiotherapy persistent pain and post-chemotherapy neuropathies due to the predominance of the neuropathic component observed in these syndromes. One study demonstrated a superiority of amitriptyline over placebo in post-mastectomy pain, with a 50% reduction in pain intensity in half of those receiving a median dose of 50 mg /day, although side effects were critical in the continuation of therapy (16). In a

controlled study, amitriptyline was ineffective in the treatment of neuropathic symptoms induced by chemotherapy (17). Nortriptyline up to a maximum dose of 100 mg / day provided a modest benefit in the same population (18). Data on venlafaxine, which should provide better tolerability due to the absence of anticholinergic effects, are conflicting. Preventive administration before surgery has significantly reduced the incidence of persistent post-surgical pain. In contrast, in a 10-week cross-over study the effect was quite inconsistent. The effect seemed to be attributable to the plasma concentrations reached, explaining the ineffectiveness in patients with lower drug concentrations (19). A certain efficacy that promised a possible clinical extension was highlighted for gabapentin (20). However, a recent cross-over study on a fairly large sample did not confirm these data with high doses of gabapentin (21). Capsacin applied at the site of the surgical wound has shown some effectiveness, but data on prolonged use are practically absent. Although opioids produce a similar benefit in a large part of non-cancer neuropathic pain syndromes, long-term use in this population is not well characterized. Surviving patients treated with opioids exhibited a hypogonadism syndrome associated with depression, fatigue, and sexual dysfunction, reversible with the suspension of treatment in relation to a possible effect of opioids on the hypothalamic-hypophysis axis (22). Although multidisciplinary treatment, with psychological intervention, is not well studied in this population, these forms are complementary to each analgesic treatment in most non-cancer pain syndromes

Pharmacology

Currently, the drugs used for neuropathic pain are classified according to the original use for which they were formulated, since the majority of these substances were not produced for an analgesic purpose. This classification is inadequate, since substances belonging to the same class act with quite different mechanisms. On the other hand, as previously reported, even a possible subdivision according to the mechanism of action is not decisive, even if it remains useful in seeking a rational approach. Therefore, a traditional distinction will be maintained between the various classes of drugs, emphasizing the possible spectrum of action according to the mechanism of action. In the various pain syndromes the possible specific advantages for that particular clinical condition will be considered according to the data in the literature. Efficacy data cannot always be translated into a field as different as cancer pain, particularly for

complex syndromes that still require the use of opioids and the possible pharmacodynamic interactions of such drugs associated with opioids.

a) Antidepressants

The mechanisms of action through which antidepressants provide their analgesic effects are manifold. The influence of the inhibitory descending bulbo-spinal pathway, mediated primarily by mediators such as serotonin and noradrenaline, on spinal activity is well known. Some antidepressants interfere with the synaptic reabsorption of serotonin or norepinephrine, increasing their availability. It also seems that they can have an opioidergic and antiglutaminergic effect, and an inhibition effect on the sodium channels. Antidepressants also interact with histamine, muscarinic and nicotinic cholinergic receptors, contributing to the development of side effects (sedation, xerostomia, urinary retention).

The efficacy of tricyclic antidepressants in the treatment of chronic pain has been confirmed in numerous studies. Scientific evidence has highlighted that these substances possess antinociceptive activity and are effective in neuropathic pain (23). Altogether, 50-90% of patients can get a pain reduction, with a relatively low NNT, for most of the pain syndromes, such as atypical facial pain, or post-stroke central pain. Therefore, about one in four patients should have a generally favorable response to these drugs.

Data from various controlled studies indicate that tricyclics are effective for both stable pain and excruciating peaks, while it is more difficult to judge the effect on allodynia, probably because this aspect has not been taken into account in most of the studies conducted so far (3). The effective dose is in the range of 25-150 mg / day, significantly lower than the antidepressant doses traditionally used of 150-300 mg / day. The short latency of action, within a week, and the lack of effect on mood support the hypothesis of an analgesic effect independent from the antidepressive effect (24).

The mechanism most often considered to explain the analgesic properties of this group of drugs is the inhibition of the re-uptake of the main amine transmitters. Antidepressants can be divided into three categories, in relation to the degree of blockage of the reuptake of these substances, serotonin and noradrenaline: selectively serotonergic drugs (SN), those with mixed activity (SN-NA), and those with main noradrenergic activity (NA). In particular, it has been assumed that the mixed-activity drugs are the most effective and that those with the highest NA component have a higher antinociceptive effect than those with the

highest SN activity, as if the SN activity were only able to improve the NA performances.

Imipramine, amitryptiline, and clomipramine determine a balanced inhibition of amine re-uptake, while desipramine and maprotiline are more NA-selective (3). In addition to these effects, tricyclic antidepressants possess other properties, such as the blockading of sodium channels, an agonist activity on alpha-2 adrenoreceptors, an indirect action on opioid receptors, a blocking action on cholinergic, adrenergic, and histaminergic receptors, a reduction in adenosine uptake, and probably an inhibition of NMDA receptor activity (25).

	Dose (mg)	Mechanism	Side effects	Comments
Amitriptyline	10-150	Inhibition reuptake NE, 5-HT	Cholinergic effects, sedation hypotension	AAA Glaucoma, IMAO, Poor tolerance to cholinergic effects and sedation
Nortriptiline	25-150	Inhibition reuptake NE, 5-HT	Cholinergic effects, sedation hypotension	Liver function less adverse effects AAA cardiovascular disease
Imipramine	25-150	Inhibition reuptake NE, 5-HT	Cholinergic effects, sedation hypotension	AAA Glaucoma, IMAO, Poor tolerance to cholinergic effects and sedation
Desipramine	100-200	Inhibition reuptake NE, 5-HT	Cholinergic effects, sedation tremor	Liver function less adverse effects

Table 1. Characteristics of antidepressants

	Anticholinergic Dry mouth Constipation	Anti- histaminic Sedation Weight	Anti- adrenergic Hypotension Alfa-1 Alfa-2
Amitriptyline	+++	+++	+++ +
Imipramine	++	+	+++
Desipramine	+	+	+
Nortriptiline	+	+	+
Venlafaxine	+		
Trazodone		+	+++

Table 2. Receptor activity of principal antidepressants.

Amitriptyline is the progenitor of this category of drugs, and has been particularly used for post-herpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy, while it has not shown efficacy in HIV-related neuropathy. Controlled studies have shown a favorable NNT in the various pathologies (see table 1). After the absorption it is subjected to hepatic metabolism and transformed into nortriptyline. It remains the drug of first choice, due to being best-known and most used. It should be started in doses of 25 mg in the evening (10 mg in the most frail or elderly patients), increasing the doses every week up to a maximum of 150 mg, if this approach is tolerated favorably. Imipramine and its metabolite, desipramine, are often used as an alternative in relation to a lower tendency to develop side effects. Nortriptyline and desipramine are the metabolites of amitriptyline and imipramine, respectively, and appear to have less relevant cholinergic and sedative effects than progenitor molecules. The most frequent side effects of this family of drugs are those of cholinergic type, with vision abnormalities, confusion, urinary disorders, dry mouth, constipation, tachycardia, anti-histamine type, responsible for sedation, and orthostatic hypotension, due to inhibition of alpha-1 adrenergic receptors. In general, this category of drugs should be used with caution in patients with ocular hypertension, in patients with cardiovascular disease, and especially in patients receiving monoamine oxidase inhibitors (MAO), for the risk of inducing a serotoninergic crisis. All drugs in this category produce an increase in appetite (26).

Venlafaxine has a different structure than tricyclics, similar to that of tramadol. It inhibits the re-uptake of serotonin and noradrenaline. Although it has a mechanism similar to that of tricyclics, it has no anticholinergic, antihistamine, and affinity effects for alpha-1 adrenergic receptors. This profile makes the drug more easily tolerable. It is therefore

used as an alternative in doses of 75-225 mg / day. The most frequent side effects are sweating and hypertension. It has been used in diabetic neuropathy and numerous other forms of neuropathic pain (27).

Venlafaxine has been found to provide a clinical activity against oxaliplatin-induced acute neurosensory toxicity, given in doses of 50 mg 1 h prior to oxaliplatin infusion and as extended release 37.5 mg b.i.d. from day 2 to day 11, in comparison to placebo (28).

Among serotonergic antidepressants, duloxetine, with a serotonin-noradrenaline spectrum, was effective in doses of 60 and 120 mg, predominantly in diabetic neuropathy. The most common side effects are drowsiness and constipation and dry mouth. Compared to other antidepressants, it is characterized by an excellent cardiovascular tolerability (26).

In a randomized double-blind crossover trial in 231 patients with chemotherapy-induced neuropathy, duloxepine provided a greater reduction in pain intensity in comparison with placebo. No serious or adverse effects were reported in the duloxetine group, although there were more medium–severe adverse events (5).

Selective serotonin reuptake inhibitors such as paroxetine, fluoxetine, and citalopram represent a subclass of antidepressants used in neuropathic pain with greater tolerability. There is no evidence that this class of antidepressants is more effective than traditional tricyclics. In particular, unfavorably elevated NNT values were found in most studies with paroxetine and fluoxetine, of the order of 5-15 (23). Side effects are anxiety, drowsiness, and an influence on the sexual sphere. They are contraindicated in patients treated with anti-MAO, and their discontinuation must be carried out with caution, due to the possible withdrawal symptoms. Finally they require controls of liver function for the risk of toxicity.

b) Studies of cancer patients.

Antidepressants in mixed or purely neuropathic pain have been assessed. The average absolute ris-benefit ratio found in a systematic review, based on 5 studies, was 0.55. The average decrease in pain was 25%. The average absolute risk of harm for antidepressants was 0.13, implying that 13% of the patients had to stop their medication because of side effects (29). In a previous systematic review, two trials on antidepressants in cancer pain were included (1 with amitriptyline, the other with imipramine as an add-on to opioids). Neither of them reported significant differences in mean pain scores between the two groups (1).

In an open-label study on the effectiveness of amitriptyline vs. gabapentin in patients with neuropathic cancer pain, no differences in pain scores measured up to 6 months were found (30). In both groups a significant decrease in pain intensity was found. In a trial with four treatment groups (placebo, amitriptyline, gabapentin, and pregabalin), a significant decrease in pain scores occurred over time in all groups (31) with a more relevant effect with pregabalin. In another study, no difference was found between amitriptyline and placebo in a cohort of patients with chemotherapy-induced neuropathy (32).

In a trial of patients with chemotherapy-induced neuropathy, patients who received duloxetine described a greater reduction in pain intensity in comparison with placebo. No serious or moderate adverse effects were reported in the duloxetine group, but there were more medium–severe adverse events (33). In mixed or purely neuropathic pain, the combination of imipramine and gabapentin was significantly more effective than each drug separately (34).

Venlafaxine was used for oxaliplatin-induced neuropathic pain producing more complete relief of acute oxaliplatin-induced neurotoxicity than with placebo. Venlafaxine was significantly better than placebo in relieving stabbing pain, pain triggered by cold, and the functional status. After 3 months, there were more patients with grade 0 toxicity and significantly fewer patients with grade 3 toxicity in the venlafaxine arm (35).

Anticonvulsants

Many antiepileptic drugs have been used in the treatment of neuropathic pain. The inhibition of neuronal hyperexcitability occurs through different mechanisms, such as the reduction of the flows in the Na + and Ca ++ channels, a direct or indirect action on the GABA, and a reduction of the activity of the excitatory transmitters (36). The principal characteristics of antiepileptic drugs are shown in table 3.

Dintoine was the first anticonvulsant to be used for neuropathic pain. The antineuralgic action of dintoine appears to be dependent on its effects on the Na + channels and its ability to inhibit the repetitive tonic discharge of the injured peripheral afferents. It suppresses the spontaneous ectopic discharge and inhibits the release of presynaptic glutamate. It is endowed with a certain gastrointestinal toxicity and a high potential for pharmacological interaction. Its use is not supported by strong scientific evidence, although in some acute settings, intravenous administration was particularly effective (37).

Carbamazepine (CBZ) increases the inactivation of Na + channels by reducing the repetitive high frequency discharge of nerve fiber action potentials. This inactivation is dependent on the voltage of these potentials. This voltage-dependent effect explains why CBZ reduces the nociceptive tonic discharge without altering normal nerve conduction. There is also an effect on high-voltage, voltage-dependent Ca ++ channels. The CBZ also reduces the release of excitatory neurotransmitters, probably through the same mechanism.

Despite its proven efficacy in neuropathic pain, diabetic neuropathy, central pain, migraine prophylaxis, and post-herpetic neuralgia, but especially in trigeminal neuralgia, for which it remains the drug of first choice in doses of 300-2400 mg / day, chronic use has been associated with ataxia and cognitive disorders, so its use should be controlled in patients with multiple sclerosis trigeminal disorders, in which cognitive impairments can coexist. Carbamazepine has an oral availability of 70-80%, binding for about 75% to plasma proteins. The drug is metabolized in the liver by cytochrome P450 CYP3A4. In chronic treatment, carbamazepine self-induces its own metabolism. Its active metabolite, epoxide, is partially responsible for signs of intoxication and accumulates during the concomitant administration of valproate and lamotrigine. The half-life is very variable, between 1 and 2 days. Elimination is renal (75%) and fecal (25%).

In trigeminal and diabetic neuralgia the value of NNT is between 2.2 and 3.3. The initial dose is 100 mg, twice a day, to be increased according to the desired effect. It has a metabolite that contributes to increase its toxicity and the risk of cutaneous rash. The main side effects include drowsiness, nausea, and ataxia, and more rarely leukopenia, hepatic damage, and hyponatremia, attributed to inappropriate secretion of ADH. Bone marrow toxicity occurs in 1-2% of patients, and therefore requires biochemical monitoring at the start of therapy and then at three months. It also has a propensity to interact with numerous drugs (36).

Oxacarbamazepine (OXC) is an analogue of CBZ which has a better tolerability profile. Unlike CBZ, which is metabolized in the oxidative pathway, OXC is reduced to a monohydroxide derivative, responsible for most of the clinical effect. OXC and its metabolite exert the same effects as CBZ. It seems to have an effect on the channels of Ca ++ even more relevant and therefore possesses the mechanistic potential to modulate peripheral and central sensitization. It has been used positively in trigeminal neuralgia, post-herpetic neuralgia, and diabetic neuropathy. OXC seems better tolerated than CBZ. The usual dose is 300 mg twice a day. The most fearful effect is the development of hyponatremia (37).

Sodium Valproate is an old generation anti-epileptic drug used especially in infantile epilepsies. The action is performed by inactivating the Na + channels, reducing the repetitive high frequency discharge of the action potentials of the nerve fiber, and encouraging an increase in the production of GABA levels through an enzymatic effect. It also induces an increase in appetite. The dosages used are between 200 and 600 mg. It has numerous pharmacological interactions (36, 37).

Topiramate (TPM) is a more recent anticonvulsant that has shown some efficacy in neuropathic pain in doses of 25-800 mg / day. The absorption is quite good (80%). Protein binding is poor. Hepatic metabolism of TPM is quite slow and is eliminated mainly via the urine. It has multiple mechanisms of action, inhibiting the Na + channels and therefore limiting the repetitive discharge, strengthening the activity of the GABA, and antagonizing some receptors to excitatory activity. In addition to the central effects, weight loss was reported for prolonged treatments. It has been used predominantly in diabetic neuropathy and to a lesser extent in other forms of neuropathic pain. An initial dose of 25-50 mg in the evening is suggested, to be progressively increased up to 200 mg (38, 39).

Lamotrigine (LMT) acts by stabilizing the inactivated conformation of the Na + channels and by inhibiting the repetitive discharge of action potentials in conditions of prolonged depolarization, consequently reducing the release of excitatory amino acids at the presynaptic level. It probably also exerts a modulating action on high-threshold Ca ++ channels. It is effectively absorbed in the gastrointestinal tract and 55% bound to plasma proteins, with a volume of distribution of approximately 1.1 L / kg. It is conjugated in the liver and has a long elimination half-life. Efficacy seems quite variable in the studies conducted so far, although some studies have reported a favorable NNT of 2.1, associated with CBZ in trigeminal neuralgia. Positive studies have also been reported in diabetic neuropathy, post-stroke central pain, and intractable sciatica, while in another study of patients with various forms of neuropathic pain or with trigeminal neuralgia, it was not superior to placebo (40). The use of LMT requires very slow titration times, starting with 25 mg for the first two weeks, to avoid the dreaded skin consequences, up to the maintenance dose of 100-200 mg / day, although sometimes doses of 400 mg / day have been used. Its action is dependent on the dose and the plasma concentrations reached (41). The most frequent side effects are drowsiness, nausea, and constipation. It is sensitive to the interaction with some antiepileptic drugs, often used in combination, such that the necessary dose is significantly higher if administered with dintoine, CBZ,

or barbiturates, which act as enzymatic inducers, significantly reducing the half-life. Valproate, on the other hand, increases the half-life of LMT.

Baclofen is a GABA receptor agonist, used particularly in trigeminal neuralgia, providing important benefits (NNT 1.4). It is particularly used for spinal treatment for spasticity (42), but is not used in cancer pain. It is used for hiccup linked to a diaphragmatic hyperactivity in doses of 10-15 mg / day.

Gabapentinoids, which currently include gabapentin and pregabalin, are currently the most used drugs if not for superior efficacy compared to other drugs, for their manageability, tolerability, and above all for the absence of interactions with other drugs. Gabapentin (GBP) is structurally analogous to aminobutyric acid (GABA). The mechanisms of action responsible for the effects produced by this substance remain to be clarified. The effect on the gabaergic system seems to be irrelevant, while an action on the subunits of the voltage-dependent Ca ++ channels at the medullary level called α2-δ, with the consequent prevention of the release of excitatory neurotransmitters, is more likely. Numerous studies have shown efficacy in some neuropathic syndromes, such as complex regional syndromes, multiple sclerosis, and in particular post-herpetic neuralgia and diabetic neuropathy with doses of 2400-3600 mg / day. Symptoms and signs of neuropathic pain, such as allodynia, burning, and hyperalgesia, improved significantly with GBP titrated up to 2400 mg compared to placebo (43,44). The effectiveness, expressed in terms of NNT calculated from the various controlled studies, is about 4 (41,42).

Some associated variables such as quality of life improved in most studies. GBP has a very interesting tolerability profile due to the absence of possible drug interactions. GBP is eliminated by the renal route, so patients with renal impairment, and among these patients with diabetic neuropathy, for example, should be subjected to reduced doses or longer intervals. Side effects are dose-dependent and mainly represented by ataxia and drowsiness. The recommended titration includes initial doses of 300 mg, increased every 2-3 days, with periods of stabilization or dose reduction due to the appearance of side effects, up to a dosage of 1500-1800 mg. An absolute failure at this dosage is a negative prognostic for further dose increases.

Pregabalin is a more potent analogue, with an analgesic effect similar to the parent molecule, but with greater dosage flexibility during titration. The mechanism of action appears to present a linear pharmacokinetics with a bioavailability of about 90%, independent of the dose, differently from gabapentin whose absorption depends on a transport mechanism in the intestinal tract.

It does not bind plasma proteins, does not undergo hepatic metabolism, and is completely eliminated in the urine. Therefore, in the presence of renal insufficiency, appropriate precautions regarding dosage should be taken. For patients with a clearance between 30 and 60 ml / min a 50% reduction of the dose is recommended. The initial dose of 25 mg is increased over a few days up to 150-300 mg / day. Most of the studies conducted so far have shown an effectiveness that can be compared to that of gabapentin (45).

Combining opioid analgesia with anti-epileptics did not significantly improve pain relief in patients with cancer-related cancer pain, although some benefit in patients with definite neuropathic cancer pain cannot be excluded. The choice should be highly individualized to balance the possible benefit against the increased risk of adverse effects of a combination therapy. The selection among antiepileptic drugs is based on the final result, including efficacy and side effects, potential for drug interactions, and costs. CBZ and PHT induce frequent gastrointestinal disorders and somnolence in about 1/3 of patients with neuropathic pain, and can create significant problems with the administration of many drugs, particularly female hormones used for contraception. GBP and pregabalin are more tolerable and safe in patients taking other drugs, due to the absence of possible interactions, particularly important in cancer patients forced to take a myriad of drugs. For this reason they are included in the first band of drugs for neuropathic pain (8). There are many concerns about the cutaneous effects of LMT and weight gain associated with TPM.

	Dose (mg)	Main mechanism	Side effects	Comments
Gabapentin	1500-2400	Inhibition of subunits Ca ++ channels	Ataxia, sonnolence	Renal elimination No interaction
Pregabalin	100-300	Inhibition of subunits Ca ++ channels	Ataxia, sonnolenza	Renal elimination No interaction
Carbamaze pine	200-800	Inhibition Channels Na + +	Somnolence, confusion, skin reactions, bone marrow toxicity	Potential for interactions Precautions for rhythm disorders and bone marrow alterations
Dintoine	300	Inhibition Channels Na +	Ataxia, confusion, tremors	Potential for interactions Precautions for rhythm disorders

Topiramate	200-400	Inhibition Channels Na +, GABA activation	Somnolence, ataxia, confusion, loss of weight	AAA renal failure
Lamotrigine	50-400	Inhibition Channels Na +, NMDA inhibition	Somnolence, ataxia, nausea, skin reactions	Ipersensibilità cutanea Pericolosa
Valproato	300	Inhibition Channels Na +, increased levels of GABA Aumento livelli GABA	Tremors, loss fo weight, nausea	Potential for interactions Precautions for bone marrow alterations Skin reactions

Table 3. Clinical features of the main antiepileptic drugs:

a) Studies of cancer patients

Analyzing 14 studies, the average absolute risk benefit for anticonvulsants (levetiracetam, pregabalin, gabapentin, lamotrigine, sodium valproate, phenytoin) has been reported to be 0.57. The average decrease in pain intensity was 48%. The average absolute risk of harm was 0.05 implying that 5% of the patients stopped taking the medication because of side effects (29). In 10 studies with 1307 patients with mixed or purely neuropathic pain, gabapentin reduced pain intensity (41,42). Three of these studies concerned the treatment of chemotherapy-induced neuropathic pain, which reported the opposite effects. The most commonly reported side effects were somnolence (19%), dizziness (17%), ataxia (13%), and fatigue (11%).

No significant difference was found between gabapentin and placebo patients with chemotherapy-induced peripheral neuropathy but with low pain intensity (44). No difference in pain scores was measured between a gabapentin and amitriptyline (30) with both groups experiencing a significant decrease in pain intensity compared to baseline.

In a systematic review of the effect of pregabalin on neuropathic pain in patients with cancer, it was not possible to draw conclusions (1). One comparative study in patients with neuropathic cancer pain reported a higher proportion of patients with a decrease of >30% in pain intensity in the pregabalin group than in the fentanyl group, with a percentage of change in pain also greater in the pregabalin group (44). No significant differences were found in a comparison study with different doses of oxycodone–pregabalin combinations in non-chemotherapy-induced neuropathic pain (45). A significantly lower pain score compared to baseline was similarly found in patients randomized to receive placebo, amitriptyline, gabapentin, and pregabalin (31).

No significant difference in pain intensity was found with lamotrigine in comparison with placebo in chemotherapy-induced peripheral neuropathy nor in levetiracetam in postmastectomy pain compared to placebo (46).

Local anesthetics

Local anesthetics, such as lidocaine, tocainide, and mexiletine, are also classified as antiarrhythmics of class IB. In many controlled studies these substances were found to be effective in peripheral neuropathies and trigeminal neuralgia. Lidocaine is an amide-type local anesthetic, prototype of an Na + aspecific blocker, able to raise the threshold of mechanical allodynia, and reducing the afferent discharge from peripherally injured neurons. In contrast to the truncular effect obtained with the blocks, systemic lidocaine selectively blocks the ectopic discharges without altering the nerve conduction. The action site is mixed, both central and peripheral. It is metabolized in the liver and has a half-life of 1.6 hours. Possible efficacy has been observed in some studies with short-term intravenous administration (5mg / kg in 30-60 minutes), able to confer analgesic effects of longer duration than the effect expected according to its pharmacokinetics. Side effects are caused by the central nervous system and the cardiovascular system, with somnolence, visual changes, hypotension, bradycardia, and electrocardiographic changes. Its scarce oral availability does not allow its use in chronic pain. It is often used as a predictive test, so long-term clinical studies have been performed on an orally absorbable analogue, mexiletine.

Tocainide has shown some efficacy in trigeminal neuralgia, but is accompanied by serious problems, such as the appearance of blood dyscrasias and pulmonary fibrosis. Mexiletine is useful in diabetic neuropathy and other peripheral neuropathic conditions. Data are often discordant and dichotomous, producing a NNT of 10 with average dosages of 675 mg / day, with a certain efficacy observed only at high doses. The initial dose is 150-200 mg / day, to be increased at 3-4 days intervals. The most important side effects are nausea and gastric burning, in addition to the central effects. It is contraindicated in patients with rhythm disorders (6).

Antagonists of NMDA receptors

Glutamate activates two classes of receptors, metabotropic and inotropic, such as AMPA, NMDA, and kainates. There is considerable evidence that hyperalgesia and allodynia resulting from tissue or nerve

damage are not only related to the increase in nerve activity at the site of the lesion, but also depend on a superactivity of the NMDA receptors. Inhibition of NMDA receptors can occur through various mechanisms, competitive or selective or in a non-competitive form depending on the level of openness of the channels. Antagonists that completely block these receptors unfortunately exert important clinical effects, as they also block physiological activities. Inhibitors with moderate affinity, such as dextromethorphan, ketamine, and memantine, have been used in the clinic, while glycine antagonists are being tested. The selective NR2B antagonists have shown important effects on the QT interval that make it impossible to use clinically (47). Available drugs have been shown to reduce secondary hyperalgesia and wind-up phenomena.

Considering the biological similarity of such phenomena with opioid tolerance, these substances have also highlighted a certain activity in preventing or reducing the development of tolerance, particularly in the presence of a nerve injury, i.e., a neuropathic pain in which the dose curve responsive to opioids is significantly displaced to the right, as if the presence of a nerve lesion had evoked similar biological responses to those that underlie chronic opioid administration. In some respects it is as if there was the appearance of tolerance (i.e., the need for higher doses to obtain an effect) without any dose of opioids being administered (48). The main problem of NMDA antagonists is currently represented by their low therapeutic index, due to the poor tolerability at the doses necessary to reduce pain. Psychomimetic effects, in particular with memory disturbances and cognitive disorders, greatly limit their clinical use, particularly in outpatients.

Ketamine has been used as an anesthetic with particular clinical indications for its ability to preserve respiratory function and sympathetic reflexes. It binds to many sites in the central and peripheral nervous system. It has been rediscovered in the last decade for its analgesic action with sub-anesthetic doses, thanks to its non-competitive activity of blocking NMDA glutaminergic receptors, exerted by binding the phencyclidine receptor through a complex action on the ionic channels. Glutamate is the main excitatory neurotransmitter, involved not only in nociceptive processes, but also in other higher functions such as memory, perception, learning, and motor coordination. In its resting state, an NMDA receptor is inactive and does not participate in synaptic modulation because its ion channel is prevented by magnesium ions. This blockade is removed in postsynaptic depolarization, caused by the release of excitatory neurotransmitters such as substance P, favoring the intracellular flow of calcium ions. The passage of calcium determines a

state of increased cellular activity, inducing a series of phosphorylating chain reactions on protein kinases, which clinically correspond to a state of central sensitization to peripheral stimuli. The ion channel of the NMDA receptor must therefore be opened so that ketamine can act on its site located in the canal. The binding of ketamine with its receptor conditions the opening of the canal, preventing the flow of calcium and limiting the consequent cascade of intracellular signals.

As the NMDA receptor is activated only by an intense activity of synaptic transmission, rather than during a physiological activity, ketamine is more effective in limiting central sensitization, with an anti-allodynamic and anti-hyperalgesic action, rather than as a pure analgesic. Therefore it lends itself to an indication in "pathological" states, such as cancer pain treated by opioids or neuropathic pain. Experimental and clinical studies have highlighted ketamine's ability to reduce opioid-induced tolerance and hyperalgesia, probably by interfering with the phosphorylation of protein kinases, whose activation is a fundamental step in the excitatory activity induced by opioids (49) (see chapter 7 and 8).

Ketamine is metabolized by cytochrome P450, with a high hepatic extraction, mainly to norketamine and hydroxy-glutamine, which is sometimes subjected to glucuronoconjugation. The oral availability is 16% with delayed concentration peaks compared to the parenteral route. Norketamine is an active metabolite, produced in greater quantities by the oral route, probably giving ketamine an unexpected activity also by mouth, despite the first hepatic passage effect, with an overall bioavailability of 55%. It is administered orally, or via nasal, parenteral, and epidural route, while the intrathecal route is currently not recommended due to possible neurotoxicity. From a practical point of view, ketamine is administered as a parenteral infusion (the subcutaneous route is more irritating), in initial doses of 100 mg / day, in complex patients requiring an increase in doses of opioids, with difficulty in managing side effects (50). The dosage can be modified according to the tolerability, up to 300-500 mg / day. The dose of opioids is reduced consensually, trying to balance the clinical effects to achieve an optimal balance between analgesia and side effects. In some patients the desensitizing effect is long lasting, beyond the presumable pharmacokinetic presence, and it is possible to suspend the treatment, with a "burst" effect that contributes to the reduction of the opioid dosage and consequently to a better tolerability. It is often associated with midazolam, to obtain a rapid analgesia for painful procedures even in bed, particularly in children, in doses of 2 mg / kg subcutaneously. Finally, sublingual administration in 25 mg doses was

effective and fairly tolerated in breakthrough pain, particularly in patients receiving high doses of opioids or intrathecal therapy (51).

A controlled study has shown that ketamine in increasing doses up to 500 mg / day, compared to placebo, is not very effective (52). This observation is affected by the selection of patients with low levels of pain intensity, a category that does not meet the requirements for an indication for the administration of ketamine, which should be reserved for patients tolerant to high doses of opioids or in conditions of hyperalgesia. These are conditions with the typical biochemical alterations in which the inhibition of NMDA receptors can play a role (53). General use is limited by the possible occurrence of side effects. In fact, most patients develop adverse effects even at low doses, mainly characterized by confusional-excitatory state, hallucinations, floating sensations, visual disturbances, and vivid dreams as well as tachycardia and increased salivary secretions. It is contraindicated in heart disease and cerebral hypertension. The use is intended for experienced personnel. It has been used nasally for the treatment of breakthrough pain in doses of 10-50 mg, with a spray dispenser of 10 mg, to be repeated every 90 seconds, with a noticeable effectiveness within 10 minutes (54).

Cannabinoids

Cannabinoids include a number of substances extracted from cannabis. The main natural psychoactive substances are delta-9-tetrahydrocannabinol and cannabidiol, but other substances, such as dronabinol and nabilone, have also been synthesized. Of these substances are known the euphorizing effects that have made their use attractive for voluptuary purposes. Side effects include important psychic reactions (17%). The analgesic action has been studied in recent years and would depend on the action exerted on numerous systems, in particular on cannabinoid and vanilloid receptors. They possess anti-inflammatory activities and increase the release of endogenous opioids. CB1 receptors are predominantly distributed at various levels in the central nervous system, while CB2 receptors are considered peripheral and closely related to the cells of the immune system, particularly macrophages, on which endogenous cannabinoids such as anandamide act. In fact, they are also expressed in the dorsal ganglions after tissue lesions. The main function of the cannabinoid system seems to be the synaptic regulation of nerve transmission, probably involving motor activity and some autonomic functions, such as appetite, vomiting, and intestinal motility as well as

inflammatory processes and the modulation of immune activity, although the mechanisms of hese activities are unclear (55).

The substances derived from cannabis sativa, delta-9-tetrahydrocannabinol and cannabidiol have recently been marketed in the form of buccal sprays in almost equivalent doses (2.7mg and 2.5mg respectively) to overcome the important effect of the first hepatic passage of the oral route. Numerous studies have shown analgesic activity, particularly in neuropathic pain, multiple sclerosis, and rigidity (56, 57). Data on cancer pain are not definitive, particularly for the lack of clarity on the methods of administration and dosages, left to the patient's free will, and the definition of "optimized opioid therapy". A randomized, double-blind, placebo-controlled, graded-dose study demonstrated efficacy and safety at low and medium doses (58). Moreover, the long-term use was generally well tolerated, with no loss of effect. Patients did not seek to increase their dose over time, suggesting that the adjuvant use of cannabinoids in cancer-related pain could provide useful benefit (59). More recently, the use of cannabinoids did not provide analgesic advantages in comparison with placebo (60). There are inconsistent findings of the efficacy of cannabinoids in neuropathic pain and painful spasms in multiple sclerosis. There are inconsistent results on the tolerability and safety of cannabis-based medicines for any chronic pain (61).

Tetrodotoxin

Tetrodotoxin (TTX) is a natural compound of marine origin that can block sodium channels, particularly common along nociceptive fibers. In animal studies, TTX showed a certain analgesic efficacy, even if the exact mechanism has not yet been specified (62). Parenteral administration produces an analgesic effect in 4-5 days, which persists for about two weeks. In cancer pain, a controlled study with TTX given for 1-4 days was performed on 77 patients. No important differences in pain intensity were found, even if overall a reduction in pain intensity, a decrease in opioid doses, and an improvement in the quality of life were observed. The most frequent side effect was an annoying perioral sensation (63). More recently, TTX in doses of 30 μg given subcutaneously twice daily for four consecutive days provided some clinically meaningful analgesia in comparison with placebo (64).

Bisphosphonates

These drugs are primary agents in the current pharmacological arsenal against osteoclast-mediated bone loss due to osteoporosis, Paget's disease, malignancies metastatic to bone, multiple myeloma, and hypercalcemia. However, the recent recognition that bisphosphonate use is associated with pathologic conditions including osteonecrosis of the jaw has sharpened the level of scrutiny of the current widespread use of bisphosphonate therapy (65).

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate (PPi), a naturally occurring compound in which 2 phosphate groups are linked by esterification. The core structure of bisphosphonates differs only slightly from PPi. Nearly all bisphosphonates in current clinical use also have a hydroxyl group attached to the central carbon. The flanking phosphate groups provide bisphosphonates with a strong affinity for hydroxyapatite crystals in bone, while the hydroxyl motif increases a bisphosphonate's ability to bind calcium. The final structural moiety bound to the central carbon is the primary determinant of a bisphosphonate's activity for the inhibition of bone resorption, due to the presence of a nitrogen or amino group.

PPi is released as a by-product of many of the body's synthetic reactions. Thus, it can be readily detected in many tissues, including blood and urine. PPi is capable of inhibiting calcification by binding to hydroxyapatite crystals, suggesting that the regulation of PPi levels could be the mechanism by which bone mineralization is regulated. Like their natural analogue PPi, bisphosphonates have a high affinity for bone mineral because they bind to hydroxyapatite crystals. Bisphosphonate skeletal retention depends on the availability of hydroxyapatite binding sites. Bisphosphonate not retained in the skeleton is cleared by renal excretion. Moreover, bisphosphonates inhibit hydroxyapatite breakdown, also suppressing bone resorption. Bisphosphonates may also limit both osteoblast and osteocyte apoptosis. The importance of this function for bisphosphonate activity is currently unclear.

The high affinity for bone mineral rather than other tissues allows bisphosphonates to achieve a high local concentration throughout the entire skeleton. For these reasons, bisphosphonates have become the primary therapy for skeletal disorders characterized by imbalanced skeletal remodeling, in which osteoclast and osteoblast activities are not tightly coupled, leading to excessive osteoclast-mediated bone resorption.

The first generation of bisphosphonates did not contain the nitrogen group (etidronate, clodronate, and tiludronate). The second- and third-

generation bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) have nitrogen-containing R2 side chains. The mechanism by which nitrogen-containing bisphosphonates promote osteoclast apoptosis is distinct from that of the non–nitrogen-containing bisphosphonates.

Bisphosphonates are very hydrophilic substances, and are poorly absorbed from the gastrointestinal tract (<1% for an oral dose). The amount of bisphosphonate retained after either oral or intravenous administration varies widely both between patients and across clinical conditions and reflects individual variations in bone turnover.

A previous limitation for oral bisphosphonate therapy was the inconvenience associated with daily oral administration (remaining upright for 30 minutes and refraining from eating for both 2 hours beforehand and at least 30 minutes afterwards) and the relatively common development of gastrointestinal symptoms. More recent preparations allowing for once-weekly (alendronate or risedronate) or even monthly (ibandronate or risedronate) oral administration has profoundly affected bisphosphonate delivery for most patients. On the other hand, the availability of intravenous preparations (pamidronate, ibandronate, and zoledronic acid) has eliminated the problems of gastrointestinal adverse effects associated with oral bisphosphonates. However, the rate of acute phase reactions, including fever, myalgias, arthralgias, or headache, is increased in patients receiving intravenous bisphosphonates.

Bisphosphonate-mediated induction of osteoclast apoptosis cannot be measured directly within the clinical setting. However, a subsequent reduction in biochemical markers of bone resorption (for example amino- and carboxyl-terminal breakdown products of type 1 collagen in serum and urine) is reasonably a possible surrogate of bisphosphonate efficacy. The peak of suppression of bone resorption occurs within approximately three months after bisphosphonate therapy and remains roughly constant with the continuation of treatment. Resorption is suppressed more rapidly after intravenous bisphosphonate administration than after oral bisphosphonate therapy.

The duration of suppression is largely a function of bisphosphonate potency for mineral matrix binding. The most potent bisphosphonate, zoledronic acid, at a dose of either 4 or 5 mg effectively suppresses biochemical markers of bone resorption. The precise biologic half-lives of the last generation of bisphosphonates remain the subject of debate, due to the difficulties in determining bisphosphonate levels in urine and serum. It has been estimated that for the potent bisphosphonate alendronate there is a biologic half-life of more than 10 years after single-dose intravenous

administration.

Bone-targeted agents represent a relevant treatment option to prevent and delay scheletal-related events in patients with bone metastases secondary to solid tumors. The mainstay of treatment has been the bisphosphonate zoledronic acid, given via intravenous infusion. Zoledronic acid is commonly administered every 3 to 4 weeks over a minimum of 15 mins. This short infusion time has been considered an advantage for zoledronic acid, compared with the other available intravenous bisphosphonates that require longer infusion times. Pamidronate is given as a 2-h infusion of 90 mg every 3-4 weeks, and ibandronate is given as an infusion of 6 mg over at least 15 mins every 3-4 weeks.

The main side effects of bisphosphonate therapy are acute reactions, gastrointestinal toxicity, renal toxicity, and osteonecrosis of the jaw. Osteonecrosis of the jaw is a rare but serious complication that manifests as a painful oral ulceration that exposes the underlying bone. The pathophysiology of this clinical picture has not yet been clarified. However, risk factors include treatment with intravenous bisphosphonates, dental extractions, and the presence of oral infections. It is recommended to perform a dental examination in all patients to be treated with bisphosphonates and in patients who have been given these drugs in the last three months (66).

More recently, denosumab (a receptor activator of nuclear factor kappa-B ligand inhibitor) administered as a subcutaneous injection every 4 weeks has been introduced for the prevention in patients with bone metastases from solid tumors. An integrated analysis of three trials demonstrated that denosumab was superior to zoledronic acid in delaying the time to first skeletal event by a median of 8.2 months, and in reducing the risk of a first skeletal event by 17% (67). In a meta-analysis, denosumab was safer in delaying or preventing skeletal-related events in patients with bone metastases and prevented pain progression compared to zoledronate (68). Denosumab demonstrated improved pain palliation compared with zoledronate. In addition, fewer denosumab-treated patients shifted to strong opioid analgesic use (69).

Although the evidence to support an analgesic role for bisphosphonates and denosumab is weak, bisphosphonates and denosumab appear to be beneficial in preventing pain by delaying the onset of bone pain rather than by producing an analgesic effect per se (**70**).

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CHAPTER FOURTEEN

DRUG METABOLISM AND INTERACTIONS

Cancer patients are often treated with drug cocktails. The administration of multiple drugs can produce unexpected and serious clinically evident adverse reactions, due to pharmacological interactions. The appearance of such reactions leads to increased morbidity and mortality, as well as increasing healthcare costs. Many factors can influence the activity of a drug: age, gender, concomitant diseases, the function of excretory organs, the administration of multiple drugs, diet, and lifestyle habits. Furthermore, it has been observed that some genetic variables are able to strongly influence the pharmacokinetics and pharmacodynamics of drugs. Substantially, interactions can affect all metabolic processes that include the absorption, distribution, catabolism, and elimination of drugs. While clinical interest is often focused on pharmacokinetic factors, such as protein binding, gastrointestinal absorption, renal elimination, and synergistic drug actions, in recent years, also on the basis of pharmacogenetic information, attention has moved on ghe ability of drugs to interact with the hepatic transformation systems catalyzed by the cytochrome P450 enzyme group. A variation in DNA sequences may produce alterations in the function of a given enzyme responsible for the metabolization of a drug and thus influencing its clinical effect, with results of different intensity. Pharmacogenetics describes the genetically determined variability in drug metabolism, while pharmacogenomics is concerned with developing new drugs based on greater knowledge of the human genome (1).

General aspects of metabolism

In general, the essential function of biotransformation, which occurs predominantly but not exclusively in the liver, is to increase the hydrophilicity of a substance to facilitate its elimination. The new product may be more potent than the original substance (L-dopa becomes dopamine in the basal ganglia), be inactive (pentobarbital is transformed

into inactive metabolite), or maintain the same activity (benzodiazepines are transformed into still active compounds).

Metabolism includes two types of reactions. Phase I reactions involve microsomal enzymes to catalyze oxidation, reduction, and hydrolysis reactions, which cause structural modifications that make the drugs less toxic and more hydrophilic. This transformation allows for a subsequent excretion, although in some cases they can produce active metabolites (acetaminophen for example). Phase II reactions are catalyzed by microsomal, mitochondrial, and cytoplasmic enzymes, and involve extramolecular modifications with conjugation with endogenous substances. These reactions include glucuronoconjugation, sulfation, acetylation, and mutilation. These modifications promote the formation of a polar substance with a lower activity and a greater ease of elimination by the renal route. In some cases these products maintain a certain activity and can contribute to the clinical effect, particularly in the presence of a lower renal clearance, the last and only elimination route.

a) Phase 1 metabolism: cytochrome P450

The CYP450 consists of a group of isoenzymes such as monooxygenase, which is mainly found in the smooth endoplasmic reticulum at the hepatic and intestinal levels. Cytochrome P450 takes its name from its absorption spectrum, and provides the largest amount of enzymes of phase I.

Each enzyme group of this system is distinguished by the symbol CYP, followed by a number (which represents the family of enzymes, e.g. 1, 2, 3), a letter (an enzymatic subfamily, e.g. A, B, C, D), and another number (the individual enzyme). Their function is to metabolize endogenous substances such as steroids, lipids, hormones, and prostaglandins and to detoxify many exogenous compounds. Approximately 50% and 25% of drugs are metabolized by CYP3A4 and CYP2D6, respectively.
These enzymes can inactivate a drug, producing less active metabolites, or on the contrary can activate it. The most important isoenzymes are CYP1A2, CYP2D6, and CYP3A3/4 (2).

CYP1A2 catalyzes the transformation of many substances used in the clinical setting, such as theophylline, warfarin, and caffeine. The system is inhibited by some antibiotics, such as ciprofloxacin and erythromycin, while it is increased by dintoin, phenobarbital, omeprazole, and nicotine.

CYP2D6 is involved in 25% of the available drug transformation processes. The genotypes of this system are quite variable, not only for functional and non-functional polymorphisms, but also for gene

duplication, with a superior production of some variants typical for some ethnic groups. The subjects are subdivided into “poor, intermediate, or ultrarapid” metabolizers. This classification depends on the number of copies of alleles transmitted by the gene. In the case of nortriptyline the “poor” metabolizers do not have copies of CYP2D6, the “intermediate” have only one copy, the “ultrarapid” have two copies, and so on. CYP2D6 substrates are drugs of considerable interest, often used in combination or with other drugs in cancer pain, such as mexitiletine, tricyclic antidepressants, haloperidol, codeine, dextromethorphan, amitriptyline, desipramine , nortriptyline, and some cardiovascular drugs such as metoprolol, fleicanide, and propafenone as well as propanolol. The selective serotonergic antidepressants inhibit this enzyme system, thus increasing the effect of concomitant drugs (table 1). CYP2D6 is an easily saturable system and scarcely inducible.

Haloperidol and quinidine inhibit this enzyme system and therefore involve an increased plasma level and availability of such drugs even at lower doses. Patients with genetic defects of this isoenzyme will have less hydroxylation capacity with some drugs such as beta-blockers, antiarrhythmics, tramadol, codeine. On the other hand, 5-6% of the population show a greater enzymatic activity.

The CYP3A subfamily represents about 40-60% of the cytochrome activity, depending on the site, and is therefore responsible for the greatest amount of transformation reactions both at the hepatic and intestinal levels, with a specificity for the fairly large substrate. Contrary to CYP2D6, it is an inducible system and genetic polymorphism is less frequent (3). The main substrates are benzodiazepines, haloperidol, carbamazepine, fentanyl, alfentanyl and methadone, antifungals, many antibiotics, calcium antagonists, many statins, antihistamines, antiarrhythmics, steroids, and immunosuppressants. This broad spectrum of medications and the inducibilty of the enzyme explain the increased possibility of a competitive interaction, depending on the concentration of drugs, on the affinity of the enzyme to the substrate, and on the co-administration of agents capable of inducing the activity of the enzyme.

-Facilitators and substrates

Drugs are substrates for an enzyme. In some cases they inhibit or induce the activity of the enzyme, that is, they increase or reduce the effect of another substrate. The concentration of the substrate increases (if the facilitator is an inhibitor) or decreases (if the facilitator is an inducer). Many drugs possess both functions, according to the presence of a different

compound in association. They can act as targets or facilitators, depending on the combination of substances taken together at the same time. Erythromycin, for example, has a dual function as substrate and inducer of CYP3A4. Methadone and carbamazepine are inducers for their own CYP3A4 enzyme, meaning they are able to induce their own metabolism.

	Facilitators	Substrates
Inhibitors	*Inducers*	Antiarrhythmics (flecainide, mexitiletine, propafenone)
Fluoxetine	Antitubercolar drugs	Antipsychotics (haloperidol, risperidone)
Paroxetin	Isoniazide, rifampicine	Beta-blocking agents (metoprolol, propanolol)
Sertraline		SRRI (fluoxetine, paroxetine)
Haloperidol		Tricyclic antidepressants
Chinidine		Analgesics (codeine, dextropropoxyphene)
		Fenformine
		Venlafaxine

Table 1. CYP2D6 facilitators and substrates

-Enzymatic induction

The induction of an enzymatic system occurs when a drug stimulates the synthesis of more enzymatic proteins, thus increasing the inactivating capacity, and therefore resulting in a reduction of the clinical effect of the drug. The most important isoforms from the clinical point of view are CYP3A3 and CYP3A4, the latter being the predominant form. Many drugs, such as benzodiazepines, antidepressants, corticosteroids, and anticonvulsants, induce CYP3A4, sometimes without being the substrate. Some substances, such as methadone and carbamazepine, can self-induce the activity of the enzyme. Some herbs, e.g. ginseng and St. John wort, are potent inducers of CYP3A4.

Carbamazepine, dintoin, phenobarbital, and primidone stimulate the activity of many enzymatic systems, such as CYP1A2, CYP2C9, CYP2C19, CYP3A4, glycuron-transferases, and hydrolysis epoxide, involved in various ways in the transformation of many drugs, reducing their effectiveness. Carbamazepine can potentially decrease the effect of various drugs by reducing their plasma concentrations by enzyme induction (facilitator-inducer) or increasing the transformation of a drug to an active metabolite. For example, it can reduce the concentrations of

some benzodiazepines but increase the concentration of their active metabolites (4).

On the contrary, for drugs that are transformed into more active or toxic substances, the interaction can induce an unexpected increase in the effect, due to an increase in blood concentration as, for example, in the transformation of primidone into phenobarbital in the presence of dintoin. Oxacarbamazepine, lamotrigine, and topiramate, albeit to a lesser extent, can perform an inductive action and be themselves prey to other inducers. The clinical relevance is often not important due to a sort of compensation between two substances with the same effect, for example antiepileptics, present at the same time.

Of course, the problem may arise paradoxically at the discontinuation of one of the two drugs, for the break of a fragile equilibrium with an increase in the concentrations of a drug no longer subjected to intensive metabolization.

	Facilitators	**Substrates**
Inhibitors	*Inductors*	
SSRI	Anticonvulsants	Antiarrythmics
Antifungal agents	Antitubercolar drugs	Antidepressants
Valproic acid		Benzodiazepines
Cimetidine		Ca-antagonists
Diltiazem		Immunosuppressants
Omeprazolo		Acetaminophene
Chinidine		Enalapril
Antiviral drugs		Antiviral drugs
		Theofylline
		Warfarin
		Estrogens
		Omeprazol
		Eritromicine
		Codeine

Table 2. Facilitators and substrates of CYP3A3/4

-Enzyme inhibition

The inhibition of metabolism by a substance leads to an increase in the concentration and therefore an increased activity of the drug, with a consequent effect higher than the expectations for that given apparently therapeutic dosage. The mechanism is competitive if the facilitating substance binds the active site on the substrate of the involved isoenzyme, as in the case of cimetidine, ketoconazole, or macrolides. The non-competitive mechanism provides that the enzyme is modified or

inactivated in such a way as not to be able to attack the substrate, as in the case of spironolactone and chloramphenicol, which form intermediate suicide metabolites that inactivate the cytochrome, and leave the substrate free.

The inhibition of the enzymatic system can be dependent on competition between two or more drugs that use the same enzyme or for a permanent inactivation. Enzyme activity is reduced by facilitators-inhibitors such as imidazole antifungals, oral contraceptives, cimetidine, macrolide antibiotics, and serotonergic antidepressants, which are therefore able to produce an increased effect by reducing the biotransformation of target substances. Grapefruit juice carries out an inhibiting action on CYP3A4 directly, limiting the availability for other drugs, thus increasing their clinical effect.

Valproic acid differs from other antiepileptics due to its tendency to inhibit the oxidation of phenobarbital, the glucuronidation of lamotrigine, and the transformation of carbamazepine into epoxide.

Clinical aspects of drug interactions

The use of analgesic or adjuvant drugs used in cancer pain can be complicated by the possible interference between several substances, frequently used concomitantly. The administration of two or more drugs, or even the concomitant administration of some foods or herbs, often involves a possible pharmacological interaction, which is expressed in a reduction or an increase in the expected effect. While most of these phenomena do not reach an evident clinical effect, in some cases they can result in clinical situations that are as unpredictable as they are dangerous.

The peak effect of an interaction is reached after a few days, approximately 4-5 half-lives, equivalent to the achievement of steady state. The duration of the interaction is also dependent on the half-life of the drug that requires a few days for its removal. Non-competitive inhibition requires more time for enzyme regeneration.

The combination of genetic polymorphisms and drug interactions can lead to a multiplication of effects on the elimination of a drug. Drugs can inhibit or induce the metabolism of other drugs administered simultaneously. A drug such as risperidone can be metabolized by various isomers, such that an inhibitor of only one system will interfere to a lesser extent, as it is functionally replaced by the alternative system of elimination.

Ketamine	Diazepam	prolonged effect
Fentanyl, methadone	Carbamazepine, dintoin, rifampicin	reduced effect
	Azoles	increased effect
Morphine	Cimetidine, alcohol, Antidepressants	increased effect
Benzodiazepines	Cimetidine, ranitidine, azoles, verapamil	increased effect
	Barbiturates	reduced effect
Antidepressants	SSRI, cimetidine, chinidine	increased effect
	Barbiturates, dintoin, carbamazepine	reduced effect
Barbiturates	Dintoin	decreased effect
Carbamazepine	Cimetidine	increased effect
	Dextropropoxyphen	increased effect
	Ca-antagonists	increased effect
	Dintoin	reduced concentration, increased metabolite concentration
	Lamotrigine	increased metabolite concentration
Dintoine	Cimetidine, omeprazolo, fluconazol	increased effect
	Lamotrigine	reduced effect of lamotrigine
	Valproic acid	reduced effect of valproic acid, increased effect of dintoin
Valproic acid	Eritromicine, isoniazide	increased effect
	Lamotrigine	increased effect of lamotrigine

Table 3. Most common interactions of drugs used to treat cancer pain. When not indicated, the effect refers to the first drug.

Pre-hepatic interactions

Phenytoin binds to some microelements, iron, calcium, magnesium, sucralfate, and cholestyramine, resulting in less absorption than the administered dose and, for example, the losing of its anti-epileptic or co-analgesic properties. Therefore, its administration should take place at different times. Failure to absorb a substance may be promoted by a concomitant medication. For example, antacids alter the gastric pH, reducing the absorption of drugs such as quinolones and cephalosporins. A

competitive placement from the carrier proteins is a possible cause. However, the possible interaction is clinically negligible, due to the protection of redistribution and effective elimination, unless there is a high protein binding, a small volume of distribution, a slow elimination, or a narrow therapeutic window. Albumin and α-glycoprotein are the main transport plasma proteins on which most of the drugs compete. Amitriptyline, many benzodiazepines, dintoin, and valproic acid have a high protein binding (95%). The combination of valproic acid and dintoin may be relevant. Dintoine has a fairly narrow therapeutic window and even small percentages displaced by other drugs may induce a significant toxicity due to an increase in the concentration of active free drug. A complex interaction is that reported between valproate and dintoin, competitive at various levels.

Intestinal metabolic function can produce substantial pre-hepatic elimination, even if this effect is saturated. Furthermore, P-glycoprotein tends to reduce the absorption of molecules that have a saturable intestinal metabolism. The inhibition of P-glycoprotein increases the fraction of substance attacked by CYP3A4. Drugs that inhibit P-glycoprotein and CYP3A4 may alter the pharmacokinetics of other drugs by reducing intestinal absorption and inhibiting biliary excretion.

Pharmacodynamic interactions

The association of several drugs with the same indication can lead to a strengthening of the effect sought, as to a greater overall toxicity. In general, the combination of drugs acting through different mechanisms is expected to be more effective, although there are no data tackling the complexity of quantifying multiple dose-response relationships.

Drugs such as anti-inflammatory or ACE inhibitors can reduce renal function and consequently reduce the elimination of certain active hydrophilic metabolites, as in the case of some opioids (see below). The most important interaction, also responsible for fatal events such as serotonergic syndrome, similar to the malignant neuroleptic forms, is certainly the one reported among monoamine oxidase inhibitors (IMAO) with agents such as dextromethorphan, serotonergic antidepressants, such as fluoxetine, and meperidine, agents able to increase the availability of serotonin. Even foods rich in tryptophan, a precursor of serotonin, during treatment with IMAO, are able to produce similar effects (5). Such factors as advanced age, comorbidity, brain tumors, and a high number of drugs are particularly associated with a high risk of drug interactions (6).

Renal elimination

Drug excretion is predominantly renal, compared to biliary secretions, plasma esterases, and other minor pathways. Renal elimination depends on various factors, such as glomerular filtration, tubular secretion, and reabsorption. The alkalinization of urine by some drugs, such as alkalizing products or furosemide, can modify the excretion of other substances. Other substances can inhibit tubular secretions and maintain high plasma concentrations of some drugs (probenecid for ketorolac and methotrexate for example, or methotrexate for pump inhibitors).

The role of nutrients

As reported, some nutrients or herbs can affect enzyme systems. Some components of grapefruit juice, for example, inhibit CYP3A3/4 and increase the activity of substances subjected to the metabolism of this system. Some herbs, used as alternative medicine, have a minimal inhibitory activity on MAO and a serotonergic activity (5).

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CHAPTER FIFTEEN

PHARMACOGENETICS

Diversities of pain sensitivity, bioavailability, side effects, tolerance, and dependency may limit the clinical application of opioids (1, 2). Polymorphisms of μ opioid receptor gene (OPRM1) and ATP-binding cassette B1 gene (ABCB1) (multidrug resistance 1 [MDR1]), as well as Catechol-O-methyltransferase (COMT) variants, have shown a significant association with opioid analgesia effects and opioid consumption (3, 4).

Polymorphisms affecting pharmacodynamic factors

a) μ -opioid Receptor (OPRM1) Gene

The μ-opioid receptor (MOR), the main target of most opioids, is encoded by the OPRM1 gene, which includes more than 100 polymorphisms. Among those polymorphisms, the SNP (rs1799971) A118G occurs in exon 1 of the OPRM1 gene, in which replacing an adenine with guanine substitutes an aspartic acid for an asparagine at a putative N-glycosylation site (N40D) such that a glycosylation site is lost. The 118G/Asp40-hMORR has a lower molecular mass and a shorter half-life of the mature form than that of 118A/Asn40-hMOP, due to differential N-glycosylation (5). Of interest, the Arg181Cys produces a death signal for MOR which may abolish or significantly reduce opioid effects in affected individuals. This is a possible explanation for inefficiency of opioids. Individuals homozygous for the mutation need a highly personalized approach to pain therapy (6).

Racial differences have been found. A significant racial diversity for the A118G polymorphism has been found, being low in African American (about 2%) and Caucasian (about 13%), with higher prevalence in Asian (about 30%) populations.

Some studies assessing an association between A118G SNP and pain thresholds, analgesic effects, and requirements of opioids have been performed. The 118G tended to be correlated with reduced analgesic effects, reduced efficiency, and much less side effects induced by

morphine and its active metabolite M6G (3, 7), suggesting a mutation association with loss of function. The dominant mutant 118G allele was found to be associated with an increased opioid consumption. Higher doses of opioids were required to obtain analgesia for patients with the OPRM1 A118G variant.

The *OPRM1* single nucleotide polymorphism (SNP), as well as the duration of morphine treatment, have been found to be associated with morphine doses in cancer patients. Patients with AG genotype c.118A>G *OPRM1* needed higher doses of morphine than AA patients. Moreover, AA patients for *OPRM1* SNP presented a lower cognitive function than AG patients (8). These findings were confuted in a subsequent work in which the SNPs analyzed did not explain cognitive dysfunction in opioid-treated patients with cancer (9).

Downregulation of OPRM1 was explored as a mechanism for opioid tolerance in cancer patients. High-doses of opioids were associated with OPRM1 hypermethylation in peripheral leukocytes. Moreover, an epigenetic regulation of OPRM1 may contribute to opioid tolerance in cancer patients. Targeted re-expression of μ-opioid receptor on cancer cells inhibited mechanical and thermal hypersensitivity, and prevented opioid tolerance. This resulted in analgesia and protection against opioid tolerance, likely due to the preservation of mu-opioid receptor expression on the cancer-associated neurons (10).

Studies of cancer pain have found that patients homozygous for the 118G allele (GG) required more morphine than patients homozygous for the 118A allele (AA) (1). Patients homozygous for the 118A allele (AA) possess the highest average decrease of pain after morphine therapy compared to patients with carriage of the G allele (AG or GG) (3). These data were not confirmed in other studies (7). Moreover, the combined effect of SNPs in multiple genes has been explored. Carriers of COMT A allele (Val) and OPRM1 G allele needed the lowest morphine dose to achieve pain relief (1). The carriage of the variant OPRM1 118G allele (AG or GG) combined with that of the variant ABCB1 3435C alleles (CT or CC) for the ABCB1 gene was associated with poor response to morphine (3). The SNP rs9479757 (OPRM1) and rs7824175 (OPRK1) had a significant association with residual pain in cancer patients receiving morphine (11). In other studies investigating 112 SNPs in 25 genes, including OPRM1, OPRD1, OPRK1, COMT, and ABCB1, no association with analgesic requirements was found in a large number of cancer patients (12). Similarly, no differences in the morphine consumption related to the 172G>T, IVS2 + 31G>A, and IVS2-691G>C SNPs were found (13).

b) Catechol-O-methyltransferase

COMT is an enzyme that metabolizes a series of neurotransmitters including dopamine, noradrenaline, and adrenaline. These neurotransmitters are involved in several processes, including pain modulation. Genetic variations in the COMT gene have been implicated in several models (14). Carriers of the COMT Val/Val and Val/Met genotypes required 63% and 23%, respectively, higher morphine doses compared to carriers of the Met/Met genotype (1). In contrast, patients with the Met/Met variant were shown to require more morphine compared with patients with the Val/Val or Val/Met variants (15). How genetic variants of COMT might affect pain perception is still debated. A complex relationship between COMT genotypes or haplotypes and pain expression has been invariably reported.

Polymorphisms affecting pharmacokinetic factors

- Drug Transporters ATP-binding cassette B1 gene

Drug transporters are important proteins that can influence the absorption, distribution, and elimination of drugs. In the gastrointestinal tract, drug transporters affect the bioavailability of orally administrated opioids, which are substrates for the transporters. The absorption could be limited in the case of efflux transporters or facilitating in the case of influx. In the blood-brain barrier, transporters might affect the distribution of opioids from the blood to the central nervous system (16). In the liver and the kidneys transporters are involved in the hepatobiliary and renal excretion of opioids and their metabolites. The ATP-binding cassette (ABC) family of efflux transporters is a major family of drug transporters (17). Many opioids, such as morphine, methadone, and fentanyl, are substrates of P-gp, and therefore polymorphisms of P-gp can affect the pharmacokinetic and pharmacodynamic profiles of these opioids (18, 19). Inter-individual variation in P-gp expression and function is well documented (20).

One possible cause for this variation is the naturally occurring genetic polymorphisms of ABCB1. Glycoprotein (P-gp), the product encoded by the ABCB1 gene, is a member of the ATP-binding cassette (ABC) transporter superfamily. As an ATP-dependent transmembrane efflux pump, it has been closely linked to resistance to substrates, limiting transporting across the blood-brain barrier and determining a decreased central analgesia. More than 50 SNPs in the coding region of ABCB1 have

been reported. Attempts to characterize the association of ABCB1 SNP with drug response, clinical outcome, and susceptibility to some diseases have been performed. Genetic variation in ABCB1 has been demonstrated to correlate with the expression and function of P-gp and subsequent analgesia activity in CNS. The C3435T SNP of the ABCB1 gene was associated with the expression of P-gp (21). In the C3435T variant carriers, especially the TT homozygotes, a higher plasma concentration of morphine was found (22), and the pain duration of TT carriers was longer than that of those with C allele. Decreased daily doses of opioids were administrated in patients with 3435T allele carriers (7). Moreover, homozygotes, but not heterozygotes, for 3435T were found to achieve a better pain relief than those homozygotes CC in cancer patients receiving morphine (3). Of interest, loperamide, a peripheral opioid used as an antidiarrheal drug, can be rapidly pumped out of CNS by P-gp. Opioid analgesia was much better in P-gp deficient mice than in wild type (WT) (23). Compared with *CC/CT*, patients with the *ABCB1 TT* genotype required higher opioids doses. Nonetheless, data were not confirmed in a large study of cancer patients (12). Methadone doses are subject to ABCB1 genetic modulations. The methadone dose was increased in carriers of the 2 copies of the AGCGC (wild type) haplotype and decreased in carriers (1 or 2 copies) of the AGCTT haplotype. The methadone dose was higher in carriers of CGT, TTC, and TGT haplotypes composed of ABCB1 C1236T, G2677T/A, and C3435T.37 (24).

Actual genetic knowledge provides information by which to pursue the computational approach to drug development. Studies of few genetic polymorphisms do not have a major clinical relevance as biomarkers. However, combining different biomarkers could be a major step toward a targeted and individualized therapy. A method for selecting appropriate opioids and relative dosages in cancer patients remains an unmet medical need. To date, functional consequences of both SNPs provided unclear and non-definitive data. No significant associations between the assessed SNPs and opioid dose in cancer pain patients were found, and hence, there was no confirming information regarding the prediction of required opioid dose using genetic profiling (9, 24, 25, 26, 27). One reasonable explanation is the interaction between known SNPs and undetected SNPs. Altered mRNA stability is also responsible for the contradiction, but it remains controversial. Further studies are required to understand the concrete mechanisms of the observed discrepancies of the functional consequence in SNPs and haplotypes.

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CHAPTER SIXTEEN

ORAL OPIOIDS

There are many opioids available orally. They are predominantly μ-agonists, presenting different pharmacological characteristics which make them completely different. The selection should be based on particular features that can amplify or reduce the effects. Opioids are metabolized through two major enzymatic systems, the cytochrome CYP450 system and the glycuronoconjugation system (1). The metabolism of opioids produces substances that have a clinical effect that is sometimes superior to the parent substance (1).

Codeine

Codeine has traditionally been used for mild to moderate pain as a standard drug in the second step of the analgesic ladder proposed by the WHO. It has a potency of about 1/10 compared to that of morphine. It is believed that the potency of codeine is depleted at 180-240 mg/day due to the prevalence of side effects, although this aspect has never been appropriately considered. Codeine is almost completely absorbed in the gastrointestinal tract, with a bioavailability of about 80%. It is almost completely eliminated by hepatic metabolism, and only 10% of the dose is eliminated unchanged in the urine. Codeine is conjugated mainly to codeine-6-glycuronide. The minor metabolic pathways include N-demethylation to norcodeine and O-demethylation to morphine. Analgesia depends on this reaction, since codeine exerts a weak effect on μ receptors compared to morphine. Therefore, codeine is a prodrug without analgesic activity, which requires an adequate metabolization to be transformed into sufficient quantities of morphine (2). This transformation depends on CYP2D6, and therefore also on the expressive capacity of this enzyme, which has a certain variability. A phenotype with poor metabolic activity leads to a reduced analgesic effect, due to the scarce production of morphine. About 7-10% of subjects are in fact poor metabolizers, producing less morphine, and consequently a lower analgesia. In subjects with a poor activity of this enzymatic system (poor metabolizers), a limited codeine analgesia has been

observed compared to patients with normal activity, even if minimal analgesic activity was also proposed by codeine itself or codeine-6-glucuronide. Other substrates or inhibitors of CYP2D6 may also interact with codeine metabolism and thus influence analgesia, substrates such as chlorpromazine, haloperidol, antidepressants, and especially serotonin reuptake inhibitors. Quinidine completely prevents morphine transformation and minimizes codeine analgesia (see chapter 14).

Since most clinical effects are produced by morphine transformation, the clinical activity will in turn depend on the excretory capacities for the metabolites of morphine. Patients with renal failure on dialysis may develop significant toxicity after codeine or di-hydrocodeine. There is not much data on the capacity of dialysis to remove the drug. Codeine has antitussive and antidiarrheal effects at lower doses, regardless of its O-demethylation. In fact, these effects are also present in the various genotypes of CYP2D6 (3).

Tramadol

Tramadol presents a racemic structure composed of two enantiomers that contribute to analgesia through different mechanisms. Tramadol (+) and its metabolite O-desmetil-tramadol (M1) are μ-agonists. Tramadol (-) inhibits the reuptake of serotonin and noradrenaline, increasing the inhibitory effects on pain transmission at the medullary level (see chapter 7).

The complementarity and synergistic actions of the two enantiomers increase analgesia and the tolerability profile, especially for respiratory depression and gastrointestinal effects. The oral absorption is high, faster with drops than the capsules, and the bioavailability is 70-80%, following a first pass effect. 60-80% of tramadol is metabolized to an active metabolite, O-demethyltramadol (M1), and about 30% is eliminated unchanged. The preferred metabolic pathway is N- and O-demethylation (phase 1 reactions) and the conjugation of O-demethylated compounds (phase 2 reaction). The reaction is mediated by the cytochrome CYP2D6, whose gene is characterized by a notable genetic polymorphism that can condition the individual metabolic profile, differentiating the “total” and the “poor” metabolizers in relation to the mutations of the corresponding alleles. The analgesic effects are higher in the “extensive metabolizers” due to the greater formation of M1, while a poor metabolization corresponds to a lower production of M1, which has an opioid-like activity about 200 times higher than the original molecule (3).

M1 in fact activates μ-receptors more than the parent molecule. The enantiomer (+) has the greatest affinity with the μ-receptor. The most

frequently reported interactions are those with cimetidine and carbamazepine. The enantiomers (+) of tramadol and M1 are potent inhibitors of serotonin uptake, while enantiomers (-) are important inhibitors of noradrenaline reuptake. Therefore, the use of certain substances can influence the clinical effect. Ondasetron, which inhibits the serotonin 5-HT3 receptors, reduces the analgesic activity of tramadol, while the administration of an agonist makes analgesic doses suboptimal. In patients with limited hepatic or renal activity the elimination half-life is significantly lengthened. Therefore, tramadol administration should be problematic in patients with reduced renal activity (4). In the presence of poor activity of the excretory organs the clinical activity is prolonged. Dialysis does not significantly change the concentrations of tramadol.

The availability in various formulations, drops, capsules, suppositories, controlled release preparations, and for parenteral route, allows considerable flexibility in clinical use. Tramadol is commonly used as a second step of the ladder proposed by WHO in opioid-naive patients who have received non-opioids and/or anti-inflammatory drugs without success. Several open studies have demonstrated the efficacy of doses of about 100 mg/day up to 400 mg/day. Although higher dosages have been proposed, it does not appear that this approach is particularly advantageous. The inhibitory effects on the immune response seem lower than those reported with morphine. Considering the mechanism of mixed action, in particular the inhibition of the reuptake of mediators such as serotonin and noradrenaline, tramadol could be useful in the presence of neuropathic pain.

Tapentadol

Tapentadol is an analgesic characterized by a dual mechanism of action: a typically opioid agonist action on μ-receptors and an inhibition of noradrenaline reuptake. Agents with these properties could be useful in neuropathic pain and in enhancing opioid actions. In several studies, an efficacy comparable to that of oxycodone has been demonstrated with a better profile concerning gastrointestinal effects. Possible advantages could be a lower potential for addiction and a lower ability to interact with other drugs metabolized at the cytochrome level. In fact, the metabolism occurs through a glucuronidation process (5, 6). Some studies have shown good efficacy in the medium term, with a low tendency to increase doses and a lower capacity to determine gastrointestinal effects, probably due to the dual mechanism (7, 8). The equivalence ratio with oral morphine is around 1:3.3 (9).

	CYP2D6	CYP3A3/4	CYP2B6	UGT
Codeine	++			+
Morphine				++
Oxycodone	+	++		
Hydromorphone				++
Methadone	+	++	+	
Tapentadol				++
Tramadol	++	++		
Buprenorphine		++		+
Fentanyl		++		

Table 1. Principal metabolic pathways of opioids.

Opioid	Use
Tramadol	take care
Tapentadol	take care
Codeine	take care
Morphine	take care
Hydromorphone	take care
Oxycodone	take care
Methadone	proscribed
Fentanyl	relatively safe
Buprenorphine	relatively safe

Table 2. Recommendations for the use of opioids in patients with a poor hepatic function

Level of renal failure	*Comments*
Mild (clearance 60-90 ml/min)	Review doses of opioids with hydrophilic metabolites
Moderate (clearance 30-60 ml/min)	Problematic use of morphine, hydromorphone, codeine, tramadol, oxycodone
Severe (clearance<30 ml/min)	Lower doses of fentanyl, buprenorphine, methadone

Table 3. Recommendations for the use of opioids in patients with renal failure.

Morphine

Morphine is one of the most widely used and versatile opioids for cancer pain management. The preference for morphine is based on clinical experience, the flexibility of the doses, and the wide availability of formulations and routes of administration.

Intestinal absorption of morphine is quite unpredictable, between 10 and 50%, with variations depending on the transit and the intestinal surface available. Generally in the conversion with the parenteral route an average bioavailability of 33% (and therefore a 1:3 ratio) is calculated. Morphine has a low protein binding, strongly reduced in renal failure. Orally, in fact, the morphine undergoes a strong effect of first hepatic passage, and the availability is limited by an immediate metabolic loss along the enteroportal circle. The liver is the main site of metabolization, even if the kidney can also contribute. A small proportion is oxidized to normorphine, produced in inconsistent concentrations, but still endowed with neurotoxic activity (3). The isoenzyme UGT2B7 is the main enzyme, followed by UGT1A8 and UGT2A1, with consequent glucoroconjugation both on the pheno-hydroxyl group in position 3 and on the alcohol-hydroxyl group 6, with production of M3G and M6G, respectively. The ratio of M3G to M6G is about 7:1. Therefore, the main metabolite of morphine is M3G, which unlike M6G is not a μ-receptor agonist. Both molecules are very hydrophilic and persist for a long time, pass the hematocerebral barrier slowly and with difficulty (1/60), and can be eliminated exclusively by the kidney (1). The lower values of volume of distribution of glycuronides with respect to morphine mean that the concentration of M6G and morphine are similar, even if in reality the body amount of M6G is only 10% of the existing morphine. M6G, already 10-60 times more powerful than morphine, becomes even more powerful if injected directly at the intrathecal level. Although the affinity is similar to that of morphine, there are differences in receptor subtypes, particularly on μ2, whereby it is believed that potentially M6G can provide analgesia with inferior side effects, such as respiratory depression. The increased production of M6G by the oral route compared to the intravenous route leads to a relative increase in analgesia with long-term oral administration. Pharmacokinetic and pharmacodynamic data confirmed a variable contribution to morphine analgesia, from zero up to 66%. In contrast, the fact that M6G contributes to the toxicity of morphine in patients with renal insufficiency remains less controversial (2).

As M6G is a hydrophilic molecule, it is eliminated exclusively by the renal route, reaching high concentrations in patients with impaired renal

function and raising the risk of central and respiratory depression, despite the low propensity to pass the blood-cell barrier, beyond the different affinity on μ1 and μ2 receptors. Indeed, the transfer of M6G between plasma and the central nervous system is slow and therefore the effects can be prolonged and independent of plasma concentrations (3). However, there is no clear correlation between the concentrations reached of either morphine and its metabolites and the clinical effects. Thus, despite the evidence that M6G is a potent analgesic, it is likely that the many factors influencing the clinical response may limit the possible role of the metabolites in both analgesia efficacy and the appearance of side effects.

The conjugation mechanisms are safeguarded even in conditions of poor hepatic function. On the contrary, a reduced renal function leads to an increase in the concentration of metabolites with analgesic or otherwise toxic activity. Therefore, in the presence of a clearance of less than 30 ml/min, it is advisable to carefully monitor the dosage of morphine, lengthen the administration intervals, or better replace it with a drug with other pharmacokinetic characteristics. For their limited excretory abilities, older people are more likely to have side effects.

The possible interactions are lower in number and severity than with other opioids, and are generally of a pharmacodynamic type, rather than pharmacokinetic. Tricyclic antidepressants can reduce conjugation, while carbamazepine, phenobarbital, and dintone can induce conjugation. Conjugable benzodiazepines, such as lorazepam, may compete metabolically and result in relative overdosing. Cimetidine inhibits dealkylation, while rifampicin accelerates conjugation.

The half-life of oral morphine is about three hours, but the effect may be prolonged by the persistence of the metabolites in the plasma, especially for chronic administrations. Morphine administered sublingually or buccally is not well absorbable. The parenteral and the peridural routes have a reduced production of metabolites, at least in the short term. These differences with the oral route have been used to explain the lower toxicity with these routes of administration (see chapter 17). The parenteral route increases morphine availability, allowing the elimination of the effect of first hepatic passage typically observed with the oral route, although in prolonged administration the production of metabolites will be observed. The conversion ratio between oral and parenteral is between 3:1 and 2:1. The intrathecal route is about 100 times more powerful than the oral route, and the peridural route is about 10 times (see chapter 20). Due to its hydrophilic characteristics, morphine is easily removed by dialysis (3), with a consequent reduction of analgesia, even if the removal of M6G

is complicated by the slow removal from the central nervous system, and the effects can therefore persist for longer.

Oral morphine is available in the immediate-release form, to be administered every four hours. The night dose can be doubled to avoid interrupting sleep with the night dose. The same dose is generally administered as needed during titration or for breakthrough pain. The slow release formulation allows for more comfortable administration every 12 hours, sometimes every 8 hours. No significant differences in efficacy were found between the various oral formulations, beyond the plasma peaks, which can be reached after about an hour with immediate release morphine. Theoretically, immediate release morphine allows a more personalized titration, even if the differences do not appear relevant clinically with respect to the controlled release formulations. The flexibility of the immediate release formulation allows the tailoring of the doses in a very personalized manner even in patients with mild-moderate pain, in the so-called weak opioid area (see chapter 19a). This formulation is used for the treatment of the breakthrough with specific indications, such as a long latency or in cases of predictable breakthrough pain, administered in advance before the performing of a physical activity (see chapter 9).

Hydromorphone

Hydromorphone is a semi-synthetic opioid agonist, related to the morphine molecule (being a hydrogenated ketone of morphine). Hydromorphone is available orally in a preparation that allows a single daily administration and in some countries as an immediate release preparation . It is absorbed in the small intestine and extensively metabolized by the liver in a variety of hydrophilic metabolites, and subsequently eliminated by the renal route. About 60% of the oral dose is subtracted from the liver at the first hepatic passage, with an oral availability between 1:2 and 1:8. Thus the oral to parenteral ratio is 5:1, with a large individual variability. Hydromorphone is predominantly glucuronized to H3G and other minor metabolites by UGTs (UGT2B7). Metabolites are eliminated by the renal route together with minimal amounts of unchanged hydromorphone. H3G does not appear to possess analgesic effects. Some authors believe that it possesses excitatory properties and, like M3G, can accumulate in the presence of poor renal excretory activity, increasing the toxicity of the parent molecule (10). The use of hydromorphone in renal failure should be therefore cautious. The low volume of distribution, the high water solubility, the low molecular

weight, and the low protein binding suggest a good capacity for removal with dialysis (3).

Controlled release preparations of hydromorphone have been widely used in cancer pain. The hydromorphone OROS preparation, to be administered once a day, has a different technology, of the osmotic type, to extend the release of the substance over time. It consists of a bistrate (two-layered) active central part, osmotically active and contained in a semipermeable coating. In the gastrointestinal tract, water diffuses through the membrane in a constant manner causing a pressure increase in a controlled manner to expand the drug in this suspension and then be forced to exit through an orifice in the membrane. The tablet releases the drug independently of the acidic environment and gastrointestinal motility. This technology has already been well characterized for the administration of many drugs (11).

Oxycodone

Oxycodone is derived from thebaine, one of the alkyl-diphenyltrenics extracted from opium. Oxycodone is a μ-agonist with a lower affinity than that of morphine and methadone. The oral bioavailability is higher than that of morphine (about 60%). It has a limited fat solubility, similar to that of morphine. The protein binding is slightly higher than that of morphine (about 50%) and is not affected by the α-glycoprotein levels. The volume of distribution is similar to that of morphine (2-3 l/kg). Oxycodone metabolism is quite complex. O-demethylation is mediated by CYP2D6 to produce oxymorphone (about 10%), while N- demethylation is mediated by CYP3A4 to produce nor-oxycodone, nor-oxymorphone and other minor metabolites (approximately 45%). These enzymes present phenotypes with different activities and therefore a lower metabolic predictability dependent on the individual genetic structure. A limitation of liver function leads to higher concentration peaks and increased half-lives. Due to the phase 1 metabolic characteristics, various pharmacokinetic interactions are possible (1). Oxymorphone, an active metabolite, has a more marked affinity for the μ-receptor. Thus oxymorphone, although produced in small quantities, can influence the overall analgesia. A reduced oxymorphone metabolization by substances that inhibit CYP2D6, such as fluoxetine (see chapter 14), can paradoxically reduce analgesia or require dosages greater than oxycodone.

Another possible interaction may occur with antidepressants, with an increase in serotonin concentrations due to the competitive effect on CYP2D6. While oxycodone and noroxycodone are eliminated with urine,

oxymorphone is excreted in the conjugated form. In the presence of a reduced renal clearance, oxycodone, noroxycodone, and oxymorphone are eliminated more slowly. Oxycodone has shown similar efficacy to that of other opioids, such as morphine and hydromorphone. Many studies seem to support the hypothesis that oxycodone has a discrete affinity for the κ receptors. The equianalgesic ratio with the oral morphine derived from these studies is between 1.5 and 2, probably due to the greater bioavailability. Various preparations exist, such as a controlled release preparation at various dosages, or combined with paracetamol in fixed doses, in the form of immediate release tablets. The controlled release preparation is absorbed in a biphasic manner, with an immediate absorption of about 35% of the dose, and a residual absorption of the remaining 65% in a slower manner. The combination with naloxone in a 2:1 ratio in a controlled release preparation is a technological innovation that allows the maintenance of an adequate central analgesia, minimizing the intestinal peripheral effects and therefore reducing the constipation effect (12). Naloxone performs a competitive activity at the level of intestinal opioid receptors and is absorbed in a negligible way (2%), being metabolized by an extensive first hepatic passage through conjugation mechanisms. For high doses (over 120/60 mg of oxycodone/naloxone), naloxone absorption due to saturation of conjugation mechanisms is more likely and may produce some competition for the analgesic effects.

Hydrocodone

Hydrocodone is a semisynthetic opioid derived from codeine. It has been available in association with different amounts of acetaminophen. Currently, different formulations of hydrocodone have been developed. The spheroidal oral drug absorption system technology is characterized by extended-release beads that are prepared using sugar and starch spheres, upon which a drug excipient layer is coated, followed by an ammonium-methacrylate copolymer coating. After rapid dissolution of the hard gelatin capsule shell, the permeability of the ammonium-methacrylate copolymer coating allows gastrointestinal fluid to enter the beads and solubilize the drug. The active medication diffuses out of the beads at a predetermined rate. This entire process prolongs the dissolution of the drug and extends its absorption. This allows for both the immediate-release and delayed-release of hydrocodone for twice daily dosing. A long-acting hydrocodone tablet given twice daily has been formulated as a tamper-deterrent formulation. The dosage of extended-release hydrocodone, expected to be 45 mg or 50 mg per day, is equivalent to about 90-100 mg/day,

approximately. Other long-acting hydrocodone products are going to be developed, with a once-daily formulation which should be impossible to crush, chew, or dissolve (13). Various prodrug compounds, not available for clinical use, have been formulated to produce lower bioavailability if injected or snorted. At higher doses, saturation of the biological conversion process is believed to occur, preventing the "rush" abusers seek from opioids like hydrocodone. The pharmacokinetics is not entirely understood. Its primary metabolites are nor-hydrocodone (via cytochrome P450 [CYP3A4]) and hydromorphone (via CYP2D6). The active metabolite hydromorphone is more potent than hydrocodone, and also more bound to μ-opioid receptors than hydrocodone. Thus, patients who are ultrarapid CYP2D6 metabolizers may convert significantly more hydrocodone into hydromorphone, with a net effect of an increased analgesia. On the contrary, poor CYP2D6 metabolizers would expect a poor analgesia, except at higher hydrocodone doses (13). Hydromorphone undergoes glucuronidation, producing hydrophilic metabolites finally eliminated by the kidney. Sensorineural hearing loss has been reported as a rare adverse effect in patients taking hydrocodone, especially at high doses. Hearing loss does not respond to discontinuation of hydrocodone or corticosteroid therapy (14). Studies in cancer patients are lacking. The conversion ratio with morphine was found to be about 1.5 (15). The only existing studies are those of the formulation with paracetamol. Both efficacy and tolerability were comparable between codeine/paracetamol and hydrocodone/paracetamol in patients with moderate or severe cancer pain (16). In another study, codeine and hydrocodone produced similar analgesia but less adverse effects than tramadol (17).

Oxymorphone

Oxymorphone is one of the oxycodone metabolites, more lipid soluble than morphine or oxycodone, resulting in a more rapid transfer across the blood–brain barrier. Oral bioavailability is poor, only 10%, because of extensive first-pass elimination. Extended release oxymorphone is a new tablet formulation of oxymorphone that utilizes controlled-release technology, inserting the opioid into an agglomerated hydrophilic matrix which releases the drug as water penetrates the matrix to sustain plasma levels during the 12-hour dosing interval. A formulation of extended release oxymorphone designed to be crush-resistant, with a reduced potential for tampering and abuse, has been approved by the FDA.

Oxymorphone is metabolized by the liver. Plasma levels of oxymorphone metabolites (6-hydroxymorphone and oxymorphone-3-

glucuronide) increase in a linear fashion with increasing doses after both single- and multiple-dose administration (13). Cancer patients previously stabilized on oral morphine or oral oxycodone were successfully converted to extended release oxymorphone which provided adequate pain relief with comparable tolerability. Equianalgesic dose ratios of extended release morphine and extended release oxycodone were calculated to be 1.8:1 and 1.2:1, respectively (18). In a double-blind, crossover study of extended release oxymorphone with oxycodone , forty cancer patients achieving adequate pain relief were converted to the extended formulation and then crossed over (double-blind fashion) to the alternative medication. Extended release oxymorphone and extended release oxycodone provided comparable analgesia. The oxycodone-oxymorphone equianalgesic ratio was found to be 2:1 (19, 20).

Levorphanol

Levorphanol is a synthetic strong opioid that is a potent N-methyl-D-aspartate (NMDA) receptor antagonist, mu, kappa, and delta opioid receptor agonist, and reuptake inhibitor of serotonin and norepinephrine. The duration of action is generally long, varying from 4 hours to as much as 15 hours. Levorphanol has an oral to parenteral effectiveness ratio of 2:1. Its antagonism of the NMDA receptor, similar to those of the phenylheptylamine open-chain opioids such as methadone or ketobemidone, make levorphanol potentially useful for neuropathic pain, possibly also because of its action on serotonin and norepinephrine transporters, similar to tramadol and tapentadol (21) . The conversion ratio with morphine is 6:1.

It bypasses hepatic first-pass metabolism and thereby is not subjected to numerous drug interactions (22). Experimental studies have suggested that differences in the selectivity of various opioids for opioid receptor subtypes involved in analgesia may play an important role. Levorphanol potently labelled μ1, kappa, and delta receptors whereas morphine was relatively selective for μ sites. Levorphanol infusions yielded tolerance to both morphine and levorphanol, while morphine infusions selectively produced tolerance to morphine. This unidirectional tolerance might be due to the selectivity of morphine for μ-receptors compared to levorphanol's ability to interact with other relevant receptor subtypes. These observations raise the possibility that the order in which different opioid analgesics are administered may be of clinical significance (23). Data in cancer patients are poor, although levorphanol's profile makes it an attractive opioid in cancer pain management. Levorphanol shows a high

rate of psychotomimetic side effects such as hallucinations and delirium, which have been attributed to its binding to the k- and δ-receptors (21).

Methadone

Methadone differs substantially from traditional opioids due to a multiplicity of characteristics that have made it popular and at the same time little used. In addition to exerting the typical μ-agonist effect, in fact, it possesses an antagonist effect on NMDA receptors, strongly involved in opioid-induced tolerance and hyperalgesia, and an inhibitory activity, by its levorotatory form, of the synaptic reabsorption of norepinephrine and serotonin along the descending system of control (see chapter 7). Moreover, with the same affinity on the μ receptor with respect to morphine, it has a higher affinity for the δ receptors, probably involved in the μ receptor tolerance phenomena. Finally, the efficacy, the term used to identify the relationship between amount and receptor occupation to exert a certain effect, is superior to that of morphine. From these pharmacodynamic observations, it is evident that it substantially has a protective effect against the development of tolerance and therefore the need to increase the dosage over time, other than the pharmacokinetic characteristics that favor an increase in the effect for repeated administration.

The structure is very different from that of the drugs previously exposed. Oral methadone is absorbed extensively, with an oral bioavailability of approximately 80%. It is a particularly liposoluble substance and is strongly bound to proteins. It has a rapid distribution, particularly in fatty tissues, and a particularly long and variable phase of elimination (half-life 15-60 hours).

N-demethylation occurs by CYP3A4 and to a lesser extent by CYP1A2 and CYP2D6. Isoforms of CYP2B6, CYP2C9, and CYPC19 are also implicated. Given the great genetic variability of these enzymatic systems, the wide individual variability in the metabolization and the possible drug interactions are consequential. Inducers, inhibitors, or substrates of enzyme systems can influence methadone metabolism and therefore the clinical effect. In addition to initially inducing its own metabolism, some drugs may subsequently induce a CYP2D6 auto-inhibition, increasing the activity of substrate drugs of the same enzyme (see chapter 14). The best known agents to consider are tricyclic antidepressants, selective serotonin resorption inhibitors (SSRIs), antifungals, which can increase the effect of methadone, anticonvulsants such as risperidone, and some antibiotics, which instead tend to reduce the concentration of methadone by reducing

its effect or even precipitating an abstinence crisis. The increased metabolic polymorphism is responsible for the unpredictability and variability of methadone pharmacology (1).

Renal and fecal elimination of methadone increases with chronic administration and is pH-dependent renally. Metabolites do not have a clinical effect. Methadone does not accumulate substantially in the presence of decreased renal activity. The high protein binding and the large volume of distribution make it difficult to remove with dialysis and the dosage can be kept constant (3).

	Morphine	Methadone
Oral availability	84 %	38 %
Distribution volume	4.1 l/Kg	1.8 l/Kg
Protein binding	60-90%	35%
Clearance ml/min	96 ml/min	551
Elimination half-life	30 h	4 h
Active metabolites	-	+
Equipotency	4-12	1
Influence of renal function	+	+++
Influence of live function	+++	+

Table 4. Differences in pharmacological characteristics between methadone and morphine

Methadone, like all liposoluble agents, seems to have less gastrointestinal effects, nausea, and constipation, due to low plasma and tissue concentration, and less interference with intestinal peripheral receptors. Beyond the possible pharmacodynamic advantages, methadone has pharmacokinetic peculiarities that make its use more complicated, often requiring more expertise. Due to the characteristics examined, it is unpredictable trying to establish an equianalgesic ratio with other analgesic drugs. The problems related to the use of methadone as a second choice to restore a better opioid responsiveness are discussed in another chapter (see chapters 19c and 19d).

Although not generally used as a first choice drug, methadone can be used in opioid-naïve patients at low doses, less than 10 mg/day, and titrated slowly to achieve the required clinical effect (24). In patients already receiving opioids for moderate pain, doses of 12 mg/day are as effective as other opioids used at the level of the 3rd step of the analgesic ladder (25). Compared to other opioids, a risk of prolongation of the QT

and torsaide de point tract following treatment with methadone, attributed to a blockade of potassium channels, has been described. However, these phenomena are observable in the population at risk of arrhythmias (important electrolyte alterations) and generally do not constitute an important clinical problem (26).

Oral morphine	60
Codeine	300
Tapentadol	200
Tramadol	100
Oxycodone	40
Oxymorphone	20
Hydromorphone	12
Hydrocodone	60
TD fentanyl	0.6
TD buprenorphine	0.8
Methadone	10
Levorphanol	8

Table 5. Approximate conversion rate between oral morphine 60 mg and other opioids (TD = transdermal)

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CHAPTER SEVENTEEN

ALTERNATIVE ROUTES FOR OPIOID ADMINISTRATION

The oral route is the most convenient and widespread for the administration of opioids and is generally considered the first choice (1), based on the simplicity of administration and the cost generally incurred by the majority of oral preparations of opioid drugs. However, during opioid treatment it may be necessary to choose other routes of administration than the oral route. The inability to use the oral route is the most frequent reason, due to inability to swallow, neurological derangement, or the presence of nausea and vomiting. In such conditions absorption is unpredictable with respect to the oral route, which already in itself presents considerable individual differences in absorption. The results of abdominal surgery, with large resections of absorption surfaces, can further reduce the bioavailability of the drug administered orally and also reduce the predictability of the effect according to the prescribed dose. In other words, it is difficult to predict whether the lack of analgesia can be attributed to the ineffectiveness of the dose used or to pharmacokinetic reasons, such as a decrease in absorption.

In more than half of patients with cancer pain, an alternative route of administration (2) is commonly used, particularly during the last month of life (3). Many opioids are available in different formulations and can easily be converted into parenteral equivalents if the aforementioned route is no longer usable, while in some cases along with the change of route it will be necessary to change the drug, due to the absence of a suitable preparation. Anecdotal experience also suggests the peripheral administration of opioids, based on the overexpression of peripheral receptors in the presence of inflammation. The rectal route is not taken into consideration because considered obsolete, absolutely uncomfortable, and poorly reliable.

Transdermal route

Transdermal delivery systems consist of defined-surface films that release the drug through intact skin at a programmed and controlled rate. New systems include patches that contain a matrix consisting of silicone and medication, and a control membrane. Compared to reservoir systems, this technology has a greater adherence, and therefore greater local compatibility and predictability of absorption, as well as making it impossible to extract the drug for different purposes, possible with reservoirs.

The great advantage lies in the possibility of providing opioids to patients in whom oral transit is prevented by vomiting, bowel obstruction, or dysphagia. There are no comparative studies with the parenteral route, another obvious indication for these problems, although intuitively the transdermal route may appear to be advantageous in terms of management (see table 1). Among the disadvantages are the need to use unmodifiable dosages over 48-72 hours, which is inconvenient in situations that require frequent dose changes, and the failure to maintain a stable concentration for the expected 72 hours of application in some patients, which results in less analgesia "of the last day". The number of patches to be applied is another element that conditions the use of high doses due to the need to cover a large area of the skin. The local effects of transdermal preparations, described in the form of erythema and pruritus, are quite rare.

a) Transdermal fentanyl

Fentanyl citrate possesses a high potency (about 75 to 100 times more than morphine). The transdermal system was designed to release fentanyl at a constant rate over 72 hours. Differing from the previous reservoir technology, fentanyl is dissolved in a semi-solid polyacrylate adhesive. The membrane is available in various sizes, to release multiples of dosages of 12 μg/h (about 0.3 mg/day), depending on the commercial preparation. The amount of drug released is proportional to the surface of the patch. Passage occurs by passive diffusion, due to a concentration gradient between the content of the patch and the skin. A non-porous control membrane of a copolymer of ethylene and vinyl acetate ensures that the passage from skin to microcirculation is slow. Other components are a siliconized polyester back layer and a removable protective membrane. This system allows greater adhesiveness and wearability, but above all

limits the possible illegal use of extractive type. Double matrix systems allow further system sustainability in maintaining plasma concentrations.

The bioavailability of transdermal fentanyl is about 90% (range 60-100%), with very marked individual variations. The high bioavailability suggests that the drug is not significantly degraded by the cutaneous flora or cutaneous metabolism. The Cmax is reached after 14-18 hours. The delay is attributed to the accumulation of the drug in the skin under the patch prior to the systemic spread. When the patch is used for the first time, the early steady state is reached after 16-24 hours. Once these plasma concentrations are reached, they persist for 48-72 hours. At the same dosage, plasma concentrations of fentanyl increase slowly and progressively with the number of applications to achieve stability after the second-third patch application. An increase in body temperature to above 40° C or prolonged exposure to sunlight can increase absorption significantly and induce an overdose. Sweating can increase initial absorption and at the same time can make the effect unpredictable due to the limited adhesion, greatly improved by matrix systems. The effectiveness of transdermal fentanyl remains to be clarified in dying patients who may present variables such as poor peripheral flow or a loss of thermoregulation.

Fentanyl is metabolized in the liver through cytochrome CYP3A4 to metabolites without significant clinical activity (phenylacetic, norfentanyl, p-hydroxy [phenethyl] fentanyl). The excretion of fentanyl (unchanged by 10%) and its metabolites is via the urinary tract. The elimination of fentanyl is prolonged after transdermal application compared to intravenous administration, with an elimination half-life of 27 to 35 hours after removal of the patch with multiple administrations, whereas after removal of a single patch the elimination is earlier (about 20 hours). This phenomenon is attributed to the slow disposal of fentanyl accumulated in the subcutaneous deposit. While absorption kinetics do not appear to change with age, the elimination half-life of fentanyl after patch removal is significantly greater in the elderly than in adults generally, probably due to a lower capacity for metabolization and elimination.

Inhibition of CYP3A4 by other substances may increase the effect of the drug. Strongly inhibitory drugs, such as antifungals, can increase their side effects. Inducing drugs, like rifampicin, on the contrary, can speed up the metabolism and reduce the effect. It appears to be relatively reliable in renal failure. Given the characteristics of liposolubility and large volume of distribution, fentanyl is difficult to dialyze, if not with particular filters, and therefore does not require major dose adjustments during dialysis sessions (5). However, in renal insufficiency there may be changes in

protein binding and distribution that may modify the clinical activity of the drug.

Transdermal fentanyl offers the advantage of a continuous administration of a potent opioid by a non-invasive route compared to the parenteral route, particularly in patients with difficulty in swallowing or with impairment of the gastrointestinal tract. The method of administration appears comfortable and appreciated by the most active patients. The unchangeable dosage for the expected duration of the patch before the next administration represents a problem in patients whose analgesic requests are not very stable; therefore, during the phases of adaptation, when looking for the most appropriate dosage, the use of fentanyl can be impractical.

In terms of efficacy, transdermal fentanyl is similar to morphine and fairly long-term tolerated. The lower presence of fentanyl in the intestinal receptors, both for the route of administration and for the lipophilic characteristics of the drug, seems to confer a lower attitude to produce constipation compared to morphine, especially during opioid substitution, in which an abstinence syndrome is observed at the level of intestinal opioid receptors, that translates into an unexpected improvement of bowel transit or a frank diarrhea.

The equianalgesic relationship between oral morphine and transdermal fentanyl can reasonably be placed at 1:100 (6) (see table 2). In methadone substitution, the ratio in both directions is between 1:15 and 1:20. Given the half-life of the two drugs, it is advisable to remove one from the immediate administration of the other, in both directions (7) (see chapter 19d).

b) Transdermal buprenorphine

Buprenorphine is not used orally due to its poor gastrointestinal absorption. The sublingual route is characterized by a rapid mucosal uptake with consequent plasmatic peaks which influence tolerability, particularly in the elderly. The drug has been considered an atypical opioid due to the strong receptor binding, to the antagonist properties on the receptor, and to a limited efficacy with a low-dose ceiling effect. In the last years, these observations have been questioned. In particular, naloxone is able to move buprenorphine from the receptor in a dose-dependent manner. Furthermore, the occupation of the receptor with buprenorphine does not compromise accessibility to other opioids (8). Finally, antagonism with other opioids, feared for the possible repercussions both of the passage from one drug to another and of the simultaneous

administration of two opioids, has never been demonstrated in clinical practice. The transition from fentanyl to buprenorphine in equianalgesic doses is uneventful (9), and the administration of morphine administered as needed on a buprenorphine regimen for the control of background pain is equally effective (10). Finally, as demonstrated by many studies for drug addiction cessation, buprenorphine can be effective at significantly higher doses, within the equivalent 240 mg of oral morphine (corresponding to 140 μg/h or 3.2 mg/day of buprenorphine) (11).

The availability of transdermal administration has greatly improved buprenorphine performance. This delivery system allows the maintenance of constant plasma concentrations, without the peaks frequently responsible for the occurrence of adverse events, particularly in elderly patients, and favoring the patients' acceptability more than a continuous parenteral administration. The active substance is incorporated inside a polymer matrix, with an adhesive layer with good adhesiveness characteristics. Patches of 5, 10, 20, 35, 52.5, and 70 μg/h are available. 35, 52.5, and 70 μg/h are equivalent to 0.8, 1.2, and 1.6 mg/day, respectively. The approximate equivalence with oral morphine is about 1:70 (see table 2). It is suggested to replace the patch every three days.

The bioavailability via the transdermal route is high and very similar to that found after sublingual administration (about 60%). It has a high liposolubility, similar to that of fentanyl, and a high protein binding (96%). Plasma buprenorphine concentrations progressively increase with the number of applications to achieve stability after the third application.

Buprenorphine is metabolized by an N-dealkylation process to norbuprenorphine, predominantly from CYP3A4, and as such may present problems related to interactions with drugs with the same cytochrome profile. Buprenorphine is also conjugated (by UGT2B7) and largely eliminated in the bile.

Buprenorphine is widely distributed for its liposolubility. The vast amount of enzymatic systems available makes competitive interaction or saturation of enzyme reserves unlikely. No significant clinical interactions have been described so far. However, some caution is suggested with the use of antidepressants, aminoxidase inhibitors, and active substances on the central nervous system. Metabolites are inactive substances which therefore do not influence the dosage in patients with impaired renal activity. In addition, patients undergoing dialysis treatment do not require dose adjustments between sessions because the pharmacokinetics is not substantially modified (4).

The analgesic efficacy of transdermal buprenorphine has been reported in numerous studies, in which a good tolerability profile has also been

observed with a limited incidence of constipation, even if comparative studies with other opioids are lacking. Some studies suggest a lower tendency to induce tolerance and some effectiveness in neuropathic pain. Experimental studies have shown that buprenorphine exerts anti-hyperalgesic besides analgesic effects, helping to limit the development of secondary hypersensitivity on an experimental skin lesion (12). It is believed that this effect can be attributed to the inhibitory action on κ-receptors. This data obtained in a model of experimental pain in humans should however be confirmed in realistic models of pain, as in the case of cancer pain. Some studies also suggest a lower tendency to tolerance development. The nociceptin/orphanin FQ (NOP) has been shown to be pharmacologically distinct from classic opioid receptors. At the NOP receptor, buprenorphine is a potent partial agonist (13). The NOP agonism of buprenorphine might contribute to actions of buprenorphine in pain models in vivo beside its effects on μ-receptors. Since activation of NOP receptors leads to counter-opioid actions in the brain, the opioid receptor-mediated actions of buprenorphine could be altered by the ability of the drug to co-activate NOP receptors. It has been proposed that the auto-inhibitory mechanism occurs through activation of the NOP receptor; that is, the μ-receptor mediated antinociceptive effect of buprenorphine is attenuated by its ability to concomitantly activate the NOP receptor, rather than by KOR-antagonism. Thus, activation of the NOP receptor contributes to the ceiling effect of buprenorphine or to antagonize its analgesic effect. Therefore it has been proposed that low doses of buprenorphine bind to MOR, acting as full agonist, whereas higher doses bind to the NOP receptor, displaying a bell-shape curve and decreasing efficacy in its analgesic effect. In fact, by blocking the NOP receptor with J11 compound the curve shows buprenorphine to act as a full agonist even at higher doses [14].

Finally, it has been observed that buprenorphine, compared to most opioids, has less influence on the immune response, even if this potentially beneficial property is lost for prolonged administration, as if the effect was subjected to tolerance (15).

Severe constipation
Malignant bowel obstruction
Disphagia
Nausea and vomiting

Table 1. Possible advantages and indications of transdermal route

Oral morphine mg/die	30	60	90	120	180	240
Transdermal fentanyl						
mg/day	0.3	0.6	0.9	1.2	1.8	2.4
µg/h	12	25	37.5	50	75	100
Transdermal buprenorphine						
mg/day	0.4	0.8	1.2	1.6	2.4	3.2
µg/h	17.5	35	52.5	70	105	140

Table 2. Approximate equivalence between the two transdermal drugs and morphine.

Parenteral route

In addition to being an alternative to the oral route, the parenteral route may be more effective than the oral route at the equianalgesic dosage, in some cases offering an improved tolerability and a lower intensity of side effects, and therefore improving the overall performance of the drug. This improved responsiveness has been attributed to a lower formation of active metabolites, in the case of morphine, for example, with a limitation of the hepatic first pass effect, at least initially, typically observed with the oral route, which in some cases contributes to providing greater overall toxicity (16, 17). The transdermal route can also be problematic in some circumstances where a large increase of the dosage is necessary to the presence of severe pain intensity, or in the presence of perspiration, thermal elevation, poor peripheral blood flow, or local intolerance.

In some cases the use of the parenteral route can be transitory, for example until the resolution of the difficulty that had prevented the access of drugs by mouth, as in situations where vomiting is controlled with appropriate pharmacological measures and it becomes possible to resume oral therapy (18).

a) Subcutaneous route

The subcutaneous tissue is highly vascularized and therefore represents a reliable source of absorption, with less individual variability in the bioavailability compared to the oral route. Continuous or bolus subcutaneous morphine has been used effectively in cancer pain, particularly in patients who were intolerant of, or had poor analgesic benefit with the oral route (19). The continuous route is preferable for

optimizing tolerability, which is instead limited by the plasma concentration peaks produced by repeated boluses, and favors the management at home or in hospital, limiting the number of interventions on the patient. Availability is quite high, close to that of the intravenous route, although at high doses with larger volumes, absorption capacities can be reduced (20).

There are a number of factors that influence the absorption and tolerability of drugs administered subcutaneously. The volume to be infused over time, and therefore the solvent infusion rate, concentration, compatibility, and pH are the most important factors concerning the substance to be infused. Factors related to the patient include the presence of local inflammatory phenomena producing unpredictable diffusion, blood flow and lymphatic drainage affecting the ability to remove the drug locally and spread it systemically, and the characteristics and anatomical conditions of the site, rich in fat or on the contrary small enough for cachexia or damaged by treatments or fibrotic reactions. The simultaneous administration of enzymes, such as hyaluronidase, can facilitate absorption (19).

Contraindications to the subcutaneous route are represented by local edema, coagulation abnormalities, extreme cachexia with insufficient subcutaneous tissue, poor peripheral flow, the presence of local infections or a particular cutaneous reactivity, and lack of a minimum management capacity for the preventive substitution of the administration site (1, 21).

Subcutaneous infusion is usually performed by inserting a small-caliber Teflon cannula into the thoracic or abdominal region, avoiding damaged or edematous areas. After a few days a local reaction is observed, which should be prevented by a site replacement every 3-4 days.

The most commonly used opioids for this type of treatment are morphine and fentanyl (22), while methadone is not well tolerated locally (23).

Morphine remains the most popular drug for subcutaneous administration. The constant velocity infusion allows the maintenance of adequate relatively stable plasma concentrations. To achieve an effective analgesic concentration in a short time it is advisable to administer a bolus equivalent to about 1/6 of the daily dose.

The substitution of oral morphine with morphine subcutaneously minimizes oral toxicity. The generally accepted subcutaneous and subcutaneous conversion ratio is approximately 3: 1 (1), although some individual variability is possible, particularly when switching from the oral to the subcutaneous route in patients who have received extensive intestinal resections (24). The passage to the subcutaneous route between

different drugs introduces a further variable affecting the reliability of the dosage conversion, due to the asymmetric tolerance between two opioids (see chapter 19d). There are several systems for the continuous subcutaneous infusion of analgesic drugs.

Among the most used are syringe pumps, elastomer pumps, and electronic pumps. The last named also allow the administration of analgesics as needed (patient controlled analgesia, PCA) guided by the patient with a special command (25). Continuous infusion through a syringe pump remains the most common, simple, and economical means, particularly at home or in less medicalized environments. The subcutaneous route is also used to rapidly titrate or re-titrate patients whose treatment with oral or transdermal opioids is no longer effective, usually through repeated boluses until an acceptable analgesia is reached (17) (see chapter 19a)

Often, for simplicity or limited availability of means it is necessary to infuse several drugs with the same device. It is therefore essential to consider the compatibility between the different drugs. Diazepam and dintoine in combination are generally not recommended due to their tendency to produce precipitation, while the most commonly administered drugs such as haloperidol, metoclopramide, or midazolam can be associated in the same syringe even at high doses of opioids. The need to change doses in a non-parallel manner can however affect the concomitant presence in the same syringe of drugs with different purposes.

- In the presence of permanent venous access, use the continuous intravenous route. For the boluses use a three-way stopcock or the appropriate side rubber of the infusion extensions, avoiding frequent manipulations. Significant training is necessary for family members.

- In the absence of permanent access or in a less medicalized environment, use the continuous subcutaneous route. Inspection of the site and replacement of the Teflon needle is required every 3 days, usually inserted on the most hairless surfaces of the thorax, avoiding edematous areas. Significant training is necessary for family members .

Table 3. Recommendations on the choice and management of the parenteral routes

b) Intravenous route

Like the subcutaneous route the intravenous route offers the possibility of recovering unmanageable situations with the oral or transdermal route and can be used with a wide range of drugs available with the characteristics described above. Compared to the subcutaneous route, it guarantees absolute availability by minimizing the possible impedimentary factors present with the subcutaneous route (26), such as the large volumes to be infused in certain circumstances and the factors associated with the concentration of the drug to be administered. It is currently the fastest method by which to obtain effective concentrations in the shortest possible time (see chapter 19a) (27).

The conversion ratio with the oral route is similar to that already described with the subcutaneous route (1:3) (28, 29). The peak of analgesia is reached faster than by the subcutaneous route and is related to the physico-chemical characteristics of the drug used, which conditions the rapidity of passage through the blood-brain barrier. Fentanyl, for example, has a peak in a few minutes (30), compared to methadone and morphine, whose peak actions are reached after 15-20 minutes. However, the effect of intravenous morphine is perceptible even after a few minutes, providing a useful guide for rapid titration (see chapter 19a), and an effective treatment for breakthrough pain (see chapter 9) (31).

In hospitalized patients with very severe pain or with painful cancer-related exacerbations, repeated intravenous boluses can be used to achieve the concentrations necessary to achieve analgesia (32) faster than is allowed by the subcutaneous route (see chapter 19a). Continuous intravenous administration is particularly indicated in patients with permanent central venous access, such as implanted subcutaneous ports, or peripheral implantable systems or for temporary use in a hospital setting, where the presence of venous access is considered mandatory for the treatment of emergencies.

In other contexts, such as at home, the peripheral intravenous route involves a greater nursing load and the frequent need to replace venous access, factors that make preferable the subcutaneous route. In the absence of venous accesses due to the depletion of the available assets following repeated treatments, the persisting in attempts that only cause enormous discomfort to the patient should be discouraged (33).

The intravenous route can be used temporarily, for example during a substitution of an opioid with methadone in which, however, the oral route is precluded by the presence of vomiting. Since the oral bioavailability of methadone is about 80%, continuous venous infusion, which instead requires total availability, must consensually be with a 20% reduction in

dosage, to be returned in case of a passage back to the oral route, to equal analgesic requests. Similarly, the dose of intravenous fentanyl, which may be necessary for example to achieve an effective dosage of transdermal fentanyl, is generally lower, since the transdermal availability is 60-90% (34). When the change of the patch takes place together with a change of opioid, the possibility of discordant effects compared to the expectations resulting from the conversion calculations is more relevant. This is due to the presence of two factors influencing the cross tolerance between opioids, the drug and the route of administration, adding therefore a further element of difficulty that requires a greater level of experience.

c) Peripheral opioid analgesia

While it is well known that opioid analgesia is due to an effect on the central nervous system through receptors present at the central and spinal level, there has been a growing interest in the peripheral analgesic action of opioids, in the potential attempt to minimize the central effects of this class of drugs. For example, the presence of receptors at the level of the intestinal tract and the constipation effect induced by their activation are well known. This observation has also suggested possible therapeutic solutions with the use of peripheral antagonists or a formulation that limits their presence at the plasma level and a consequent undesired central antagonism (see chapters 19b and 22b).

In inflammatory processes, opioid receptors in the immune cells of the injured tissues have also been identified. Opioid receptors are synthesized in the cell bodies of the small fibers in the dorsal root ganglion cells and are transported peripherally and centrally along the axons. Functional studies have indicated that the C fibers mediate the peripheral nociceptive effects of morphine. The occupation of these receptors attenuates the response to the nociceptive stimulus by inhibiting the release of excitatory mediators (35).

In these conditions opioids have a favored access to the receptors due to the loss of the impermeability of the perinervous fascia and the growth of nerve endings. Furthermore, silent receptors are reactivated by the lowering of the pH and the high concentrations of ATP. Moreover, their number tends to increase due to the increase in axonal transport which is increased in the presence of inflammation. The mRNA that encodes opioid receptors is in fact abundantly expressed in the dorsal ganglia. These ganglia contain the cell bodies of the primary afferent neurons where the receptors are synthesized, to be transported along the axon towards the terminations in contact with the inflamed tissue. Thus, peripheral opioid

receptors on nerve fibers are overexpressed during inflammatory processes. There is also an interaction between the immune system and peripheral nerve endings as the immune cells are able to express opioids in the inflammatory tissue, with an intrinsic cellular transcriptional capacity similar to that present in the brain areas. These peripheral phenomena present clear protective analogies to those observed for stress analgesia. The mechanisms by which opioids act on peripheral receptors seem similar to those reported for central receptors (36).

The peripheral analgesic action of exogenous opioids in the presence of inflammatory conditions has also been corroborated in human clinical trials, even if the magnitude of the phenomenon remains controversial. The question concerning the development of peripheral tolerance also remains controversial. Other studies highlight the mediation of endocannabinoids for the peripheral antinociceptive mechanisms of morphine (37). Many studies performed with the injection of intra-articular or gingival morphine have shown an analgesic effect independent of systemic reabsorption.

The use of opioids for topical application has obvious therapeutic potentialities, favoring the appearance of a good analgesia with minimal doses and a negligible systemic reabsorption and therefore a minimization of side effects. The first clinical studies in cutaneous pain ulcers were performed with aqueous solutions of morphine or heroin gel. Subsequently, a gel (intrasite) was used to debride the necrotic tissue and to favor re-epithelialization, capable of absorbing the excess of exudate and producing a moist environment at the surface of the lesion. The gel, containing 0.1% morphine, is applied on the lesion through soaked gauze. Relatively low doses compared to the systemic ones were quite effective, even if the quantities are not easily quantifiable and the inhomogeneity of the lesions treated in relation to the expected standard makes data interpretation difficult (38).

Topical methadone dissolved in stomadhesive powder (10 mg per gram of stomadhesive) was also used effectively, particularly for exudative lesions (39). Morphine has also been used topically in mucositis pain due to chemotherapy. 15 ml of a 2% solution of morphine was administered every 3 hours, six times a day, keeping the solution in the mouth for two minutes and avoiding swallowing. This treatment was more effective than a “magic” solution containing lidocaine, diphenylhydramine, and magnesium (40). This effect seems truly peripheral, since no active plasma concentrations of morphine are detectable (41).

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CHAPTER EIGHTEEN

OPIOIDS BY TRANSMUCOSAL ROUTE

The transmucosal route is one of the most recent technological innovations for opioid administration. This route allows the rapid passage of powerful substances into the systemic circulation, bypassing the gastrointestinal enteric tract and accelerating the clinical effect, factors particularly sought in some circumstances in which pain increases with respect to the background intensity in a short time and there is a need for a rapid resolution (see chapter 9). It represents a non-invasive route, compared to the parenteral route, which at the same time allows for a fairly rapid analgesia. There are several transmucosal systems available. Each of these systems presents specific ways to deliver fentanyl. All transmucosal fentanyl preparations have been shown to be more rapid and effective than oral morphine and placebo in treating breakthrough pain episodes.

Oral mucosa

The mouth has several areas for potential transmucosal administration: the best known is sublingual, which also has the greatest absorption capacity with the areas included in the buccal vestibule, cheek, and gum. The sublingual region is in fact rich in lymphatic and blood vessels and therefore allows a rapid and direct absorption into the systemic circulation avoiding the first pass liver metabolism. There are several factors that influence the penetration of substances through the oral mucosa, including the physico-chemical nature of the substance and therefore the fat solubility, molecular weight, and degree of ionization.

Fentanyl is one of the most used substances by virtue of these properties. A low degree of ionization and a remarkable liposolubility favor transmucosal passage. The increase in the pH of saliva favors the formation of non-ionized fentanyl, more easily absorbed. The final pH is actually determined by the combination of saliva and the dissolving sugary base.

The first generation of transmucosal fentanyl is represented by the transmucosal oral citrate fentanyl (OTFC). Once the substance is absorbed the removal and the passage in the circulation will depend on the blood and lymphatic flow (1). The effect appears after a few minutes, excluding the enteral passage, notoriously an obstacle to the global bioavailability of a substance. In fact, oral intestinal absorption is 25-30%.

Analgesia occurs in 15-30 minutes and persists for about two hours, usually enough time to overcome the duration of a breakthrough pain episode, with an elimination half-life of about six hours, similar to that of intravenous injection. The head of the OTFC stick should be rubbed and massaged into the inside of the cheek for 10-15 minutes, and the immediate absorption is 25% while the rest is swallowed and subsequently partially absorbed in the intestine with a new peak, delayed and blunted, which leads to more than 50% of the total bioavailability of fentanyl (2).

In some cases the clinical effect is quite early and can avoid the continuation of local rubbing. In clinical practice this allows a flexible use of even higher dosages to obtain a greater and faster effect with the suspension of the performance as soon as sufficient analgesia appears. However, this type of intervention is not well catechized and should only be used by highly skilled and accountable patients and after the effect has been well assessed by the prescriber. There are factors that oppose the proper absorption of fentanyl. The presence of mucositis and dry mouth can greatly reduce absorption and in some cases make it impossible to use (3). Patients particularly debilitated, with deep asthenia, often use it badly and abandon it before complete use, due to fatigue. The problems related to the dosage of OTFC to be used for episodes of breakthrough pain are shown in chapter 9.

A second transmucosal buccal preparation uses another technology called OraVescent (FBT). This system, reproduced in a tablet to be placed on the gingival edge for a few minutes, produces a local effervescent reaction with an initial decrease in pH, which facilitates the solubilization of the tablet, and subsequently releases CO2, producing an increase in pH of the buccal cavity, thus optimizing the absorption in the form of non-ionized fentanyl (4). Its overall availability is around 65% (5). Its efficacy and tolerability has been demonstrated in some randomized trials (6). Sublingual positioning appears equally efficient (7).

Another transmucosal modality of administration is represented by the sublingual route. Sublingual fentanyl (SLF) consists of a self-disintegrating tablet containing a substance-wrapping carrier and a mucosal agent. It melts under the tongue in a few minutes, even if the clinical effect appears after about 10 minutes. One possible advantage is

the availability of the intermediate dose (300 μg). Availability is around 65%. Its efficacy and tolerability has been demonstrated in some randomized trials (6).

There is a sublingual fentanyl formulation consisting of different layers around a core, in which the fentanyl is surrounded by an alkalizing layer which increases its solubility and dissolution (SLF2). The absorption is around 65-70%. The available dosages also allow intermediate doses. The minimum dose (67 μg), suggested for the intermediate doses, could indeed be used for patients who use low doses of opioids, less than 60 mg/d of morphine equivalents.

In the soluble film of buccal fentanyl (FBSF), the fentanyl is in a layer that is adhered to the patient's inner cheek through a film. The availability of fentanyl is around 65%.

Nasal mucosa

Another route of administration, designed for the treatment of breakthrough pain, is the nasal route, due to a highly vascularized surface with abundant venous drainage directed towards the systemic circulation, and a homogeneous temperature that facilitates the absorption capacity. The absorption depends on the mucociliary activity which tends to remove the drug from the surface. In addition to a 150-180 cm2 absorption area of the nasal mucosa, it seems that the olfactory area, strongly constituted by neuronal structures, can be considered a prolongation of the subarachnoid space due to the intimate anatomical connections. Bioavailability seems to be high (up to 80-90%), also allowing a very rapid onset of action, approximately within 5 minutes (8). Fentanyl-pectin (FNPS) has been designed to homogenize, through a gel, mucosal absorption. This system limits the absorption peaks compared to the INFS, and detemines an availability of about 65%. Many studies have shown the efficacy of FNPS in the short and long term (6).

Ketamine by nasal administration (or sublingually) is also easily absorbed nasally with puff or drops. Theoretically, the dosage is independent of the level of tolerance to opioids, particularly in patients receiving high doses of opioids for background analgesia. However, the use should be reserved for skilled physicians.

There are no comparative studies between these products, and even the transition from one system to another can be problematic. However, the substance used is always fentanyl and therefore the previous dose can be used for reference when it is necessary to replace the system for any reason. In this case, the availability of fentanyl must be kept in mind for

each product used. In the only existing comparative study, starting and multiple doses of 50 μg and 100 μg of INFS and FNPS, respectively, provided similar effects. Both delivery systems, in doses proportional to the basal opioid regimen, provided significant analgesia within 10 minutes, without producing relevant adverse effects. It is likely that the different amounts of drug absorbed, due to different bioavailabilities, were compensated by the different strengths used (9). Of interest, INFS 50 μg and FNPS 100 μg are the starting doses suggested for patients receiving 60 mg of oral morphine equivalents for background pain.

The choice of these products depends on many factors, related to ease of use, the ability of the individual to use the preparation, individual preference, predictability of absorption, and clinical and local conditions. Evaluation of the oral cavity is essential to rule out the presence of mucositis or lesions of various kinds that reduce absorption. In a specular manner the nasal lesions will contraindicate the use of nasal preparations. Therefore, in the final choice, all the circumstances that can help in choosing the best mode of administration for that individual patient must be taken into consideration (10).

	Dose (μg)	Onset	Availability (%)
Morphine	no limits	30-45’	30
Oxycodone	no limits	30-45’	40-50
OTFC	200-1600	15-30’	50
FBT	100-800	15’	65
SLF	100-800	10-15’	65-70
SLF2	67-533	10-15’	65-70
FBSF	100-800	15 ‘	65
INFS	50-200	5-10’	80-90
FPNS	100-400	5-10	65-70

Table 1. Characteristics of fentanyl transmucosal preparations in comparison with oral opioids

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CHAPTER NINETEEN

SPECIFIC ASPECTS OF OPIOID TREATMENT

CHAPTER NINETEEN A

DOSE TITRATION

The initiation of opioid therapy or a substantial change of doses and treatment represent a particularly delicate phase (1). In these cases it is necessary to balance the needs for rapid pain control with the chances of the development of adverse effects. Opioid dose titration implies a customization of the dosage in relation to the clinical conditions and the individual response (2, 3).

There are different clinical scenarios that may require different approaches. A typical and frequent condition is that of the naive patient who requires the initiation of opioid therapy. Another situation involves patients receiving either low-dose opioids or those using so called weak opioids, that is, patients who are relatively tolerant to opioids because they are already impregnated. Moreover, during a chronic treatment it is often necessary to review the dosage as a function of modification of the clinical response or changes determined by the disease. Finally, in some cases it is necessary to intervene with a certain urgency in the case of long-suffering patients with the presence of pain of high intensity. These critical conditions require some experience to settle diagnostic questions and a more intensive intervention for the clinical resolution of a rather critical situation.

1. Opioid-naive-patients
2. Patients tolerant to low doses of strong opioids or weak opioids
3. Patients tolerant to strong opioids losing analgesia
4. Patients with severe uncontrolled pain

Table 1. Different clinical conditions for opioid dose titration

a) Opioid dose titration in opioid-naive patients

Patients with moderate pain not responsive to non-opioid analgesics should be treated, according to guidelines drawn up by the WHO, with weak opioids, such as codeine or tramadol. The role of the so-called “weak

opioids", better defined as opioids for moderate pain, has been questioned in relation to the possibility of omitting the second step of the analgesic scale (4).

The omission of the second step can not be replaced by the introduction of opioid dosages generally intended for tolerant patients, for example 60 mg of oral morphine equivalents. Although these dosages are likely to be effective, they are not justified in opioid-naive patients because of the high probability of causing side effects.

The sequential approach proposed by the WHO was compared with strong opioids with equivalent doses of oral morphine of 60 mg/day. As expected, treatment with strong opioids directly seemed more effective, but the percentage of side effects was greater (5, 6). Patients already tolerant to weak opioids who start doses of 60 mg/day of oral morphine already have a high possibility of delaying titration due to the appearance of side effects (7). Thus, opioid-naive patients should not be subjected to these doses.

Rather, the use of low doses of morphine can be a practical compromise and can make the distinction between the 2nd and 3rd steps, which seems to be anachronistic. This emphasizes the importance of choice of doses, rather than the class of drug. There are good experiences that highlight that low doses of morphine, like any other opioid, are quite tolerated and facilitate titration (8, 9). In an open-label randomized controlled study, adults with moderate cancer pain were assigned to receive either a weak opioid or low-dose morphine. The primary outcome (20% of pain reduction) occurred in 88.2% of the low-dose morphine and in 57.7% of the weak-opioid group. The percentage of responders was higher in the low-dose morphine group, as early as at 1 week. Clinically meaningful (≥ 30%) and highly meaningful (≥ 50%) pain reduction from baseline was significantly higher in the low-dose morphine group. Finally, adverse effects were similar in both groups. Thus, in cancer patients with moderate pain, low-dose morphine significantly reduced pain intensity compared with weak opioids, with a similarly good tolerability and an earlier effect (10). While weak opioids still perform a legitimate function in patients with moderate pain, particularly due to their flexibility in dosing and wide availability, with the use strong opioids it will be necessary to apply a low dose initial dosing scheme and dosage in the following days in increments of 30-50%, according to clinical response. This concept can be applied to transdermal opioids, pending an adequate provision of drugs as needed (11, 12).

Morphine	15-20 mg/day
Oxycodone	10-15 mg/day
Hydromorfone	4 mg/day
Buprenorphine	17μg/h
Fentanyl	12 μg/h
Tapentadol	100 mg/day

Table 2. Approximate initial doses of opioids to administer in opioid-naive patients.

b) Opioid dose titration in already tolerant patients who are no longer responsive to weak opioids or low doses of strong opioids

1. Oral opioids

In patients already tolerant to weak opioids or low doses of strong opioids, the initiation of treatment with approximately 60 mg of oral morphine equivalents may be a good starting point for dose titration in a patient who has not yet achieved acceptable analgesia (13, 14). The simplest method, suggested by the EAPC, suggests the use of immediate release morphine, given every four hours, for a total of 60 mg/day, and an extra dose of 10 mg as needed. The dose will be reviewed every 24 hours on the basis of the clinical trend and the number of extra requests (15). In a pragmatic study, starting at an initial dose of 60 mg/day of oral morphine, 48-60 hours after, at the end of the dose titration, the average dose was 97 mg/day. Titration had to be slowed in some cases due to the appearance of side effects, but about 80% of patients were satisfied with the treatment (7). Slow-release morphine may acceptably allow for rapid pain control (8), emphasizing that titration with immediate-release morphine is not strictly necessary.

Drugs with different characteristics, such as slow-release morphine, methadone, and transdermal fentanyl, used in equivalent doses of 60 mg of oral morphine (0.6 mg/day of TTS fentanyl, 15mg/day of methadone) were equally effective when used with rescue doses of opioids during titration, as well as other opioids initiated at equivalent doses of morphine of 60 mg/day (16, 17). Therefore the initial use of equivalent doses of 60 mg/day of oral morphine seems appropriate for tolerant patients who do not respond to second step drugs. Probably the only thing necessary, regardless of the availability of fast or slower preparations, is to assure the patient of the dose as needed during the dose titration period and monitor

the clinical situation to recalculate the daily dosage after 24-48 hours, emphasizing how attention to details is more important than the choice of the drug.

Morphine	60 mg/day
Oxycodone	40 mg/day
Hydromorphone (TD)	12 mg/day
Buprenorphine (TD)	35 µg/h
Fentanyl	25 µg/h
Tapentadol	200 mg/day
Methadone	12 mg/day

Table 3. Approximate initial doses of strong opioids to be administered in patients tolerant to low doses of strong opioids or weak opioids

2. Transdermal opioids

The initial dose in unstable patients with uncontrolled pain and possibly requiring frequent dose changes is often difficult to predict given the slow changes in plasma concentration that can be achieved by definition with transdermal drugs (16). Neverthless, transdermal buprenorphine and fentanyl can be effective, obviously advocating the use of drugs as needed, particularly during the first 24-48 hours. The doses can then be calculated in relation to the consumption of drugs as needed for the dose of the following patch (17). Patients with high levels of pain intensity should not undergo initial transdermal treatment.

3. Parenteral opioids

The parenteral administration of opioids can result in rapid pain control compared to the oral route (18). This advantage is evident in the first hours of treatment, while the results become superimposable after 24 hours. Patient-controlled analgesia (PCA) is based on direct interaction with the patient. In patients no longer responsive to step 2 drugs, by using a dose of 1 mg of morphine and a lock-out of 5 minutes, and a maximum dose of 12mg/hour, a good analgesia was obtained within 24 hours, often within six hours, for a final dose of morphine converted orally to 139 mg/day (19).

The choice of the drug or the route of administration is not essential if the administration of drugs as needed, assisting the entire titration phase, is

ensured. The parenteral route can speed up the procedure. For an appropriate conversion, the oral and parenteral ratio for morphine is between 1:2 and 1:3 (20) (see chapters 16 and 17).

c) Patients tolerant to strong opioids who lose analgesia

1. Oral and transdermal drugs

In the presence of uncontrolled pain, opioid doses should be increased progressively, by 33-50% every 24 hours (7.13, 14). If pain has been previously responsive to the opioid used, an increase in the dose allows the recovery of the analgesia previously obtained. This approach can take some time. Some studies have used opioid responsiveness using the opioid escalation index (OEI), which provides a simple method for assessing the need for increased dosage over time (21). For example, the OEI of methadone is lower than that recorded with morphine, due to the different pharmacokinetic and probably pharmacodynamic characteristics (15).

Older patients require similar procedures to adults during titration, not presenting different responsivenesses in the dosage necessary for the achievement of analgesia, regardless of the well-known reduced opioid consumption due to the pharmacokinetic limits of the elderly which are able to accentuate the clinical effects of opioids (3).

The development of adverse effects may limit the possibility to increase the dose, reducing the efficacy of an opioid according to the concept of opioid responsiveness (22). This concept highlights the significant individual differences based on significant factors related to differences in genetics, to the type of opioid used, to the type of pain, to the progression of the disease, or to changes in metabolism (23).

2. Parenteral opioids

The available data on the use of parenteral opioids in patients requiring dose increases with oral or parenteral opioids are quite poor. It has been observed that with a subcutaneous infusion of different opioids at initial doses of 50-70% of the equianalgesic dose of the previous drug, a mean of 80 mg/day of parenteral morphine allowed a good analgesia to be obtained in 50% of the subjects within 48 hours, with a final dose of 135 mg/day without producing important side effects (19). Unfortunately, the variability of the choice of the day of re-evaluation (from 1 to 27 days), in which an analgesic improvement was recorded in 71% of patients, does not allow us to draw appropriate conclusions.

d) Emergency treatment for patients with severe pain

While in most cases a progressive increase in pain intensity can be counteracted by dose adjustments, with the fairly simple titration formulas described above, some patients may present very dramatic conditions, often in emergency situations, for severe and often lasting pain, mostly underestimated and/or undertreated by other doctors. Severe acute pain requires more intensive treatment than previously described techniques.

Such patients have often received treatment that has rapidly lost efficacy or may have new reasons for the aggravation of pain intensity. In most cases, however, these patients are poorly considered from the therapeutic point of view, often for long periods, with serious psychological repercussions. In these cases the optimal dose is not predictable and a titration scheme with the more traditional modalities could take many days to find a solution to a state of severe suffering. Therefore, it would be desirable to accelerate the achievement of analgesia using the quickest means, such as intravenous opioid administration, which allows rapid changes in the blood concentration of drugs and therefore a contraction of the time taken to evaluate the effect of a given dose (24). The fear of respiratory depression is not justified if the patient is monitored in an appropriate environment: a parenteral titration in naive or tolerant patients, with a mean doubling of the opioid dose compared to the baseline doses, did not produce significant changes of carbon dioxide, thus not producing respiratory failure (25). On the other hand, the presence of pain is a reassuring element, since it represents practically an antidote to respiratory depression induced by opioids (26).

In a randomized trial, morphine administered subcutaneously took a longer time than intravenous morphine to provide analgesia in patients with an exacerbation of pain (27). In particular, the effects of an intravenous bolus of 2 mg every 5 minutes and a subcutaneous bolus of 10 mg every 30 minutes were compared. Titration was stopped when analgesia was reached, after 53 and 77 minutes, respectively, with greater efficacy in the intravenous group, despite the most unfavorable starting conditions. After 24 hours no difference was observed between the two routes of administration. In a limited number of patients, the oral ratio after conversion was 6.6 with intravenous titration and 3.7 by the subcutaneous route. These data related to conversion ratios, however, are distorted by the different timings. A ratio of 3 seems more reasonable (see chapter 17). Pain intensity improved significantly after the achievement of analgesia, despite the increase in morphine doses. From the pharmacokinetic point of view, the total availability and the fastest achievement of high plasma concentrations are obtained by the

intravenous route. Although many physicians are reluctant to use such a route due to lack of familiarity, in recent years there has been a growing awareness and interest in finding fast, effective, and safe solutions for more complex situations that require intensive intervention.

Different strategies have been suggested. In patients receiving high doses of morphine (median 1530mg), intravenous morphine was given in doses of 10-20 mg every 15 minutes, doubling the dose every 30 minutes until the pain was reduced, about 90 minutes later. The subsequent treatment was based on the total dose of the bolus administered (28).

In another retrospective analysis of patients with pain greater than 5/10, repeated boluses of 1.5 mg of intravenous morphine given every 10 minutes allowed pain control in almost 80% of patients with final doses of 1.5-15 mg of morphine. Approximately one third of the patients had side effects and 10% had to stop the titration process. This approach was proportional to the magnitude of the problem, taking into account that patients with even moderate levels of pain intensity were included (29). Knowledge of opioid pharmacokinetics and clinical experience may be useful to find the most appropriate strategy. Morphine exerts its effect in a few minutes, even if the peak time of the blood and cerebral concentration, corresponding to the analgesia, is a hysteresis that corresponds to the delay in passing through the hematocerebral barrier, due to the poor liposolubility of morphine. Therefore, the clinical objective should not be the appearance of an analgesia observed in a few minutes, but the trend over time, or a moderate improvement in the intensity of pain which will then correspond to a more powerful effect after about 15-30 minutes (24).

Indeed, the use of small repeated boluses at a certain period of time will be less effective and may confuse the situation in relation to the calculation of current needs and especially the conversion to the oral route. From a pharmacokinetic point of view, this approach produces a series of curves that overlap and fragment the same time (figure 1). For example, while a bolus of 20 mg dose produces a rapid effect from which clinical judgment can be derived, the same dose administered to spaced small boluses is not able to achieve an effective blood concentration. From the previously reported series (31), the maximum administered dose of 34 mg of morphine corresponds to 23 injections of 1.5 mg repeated every 10 minutes, that is 215 minutes. During this phase, most of the morphine administered with the first boluses will have been eliminated, and the actual dose will be difficult to calculate. This reasoning explains the subsequent, truly unusual, and clearly misleading relationship of a conversion ratio with the oral route of 1.1.

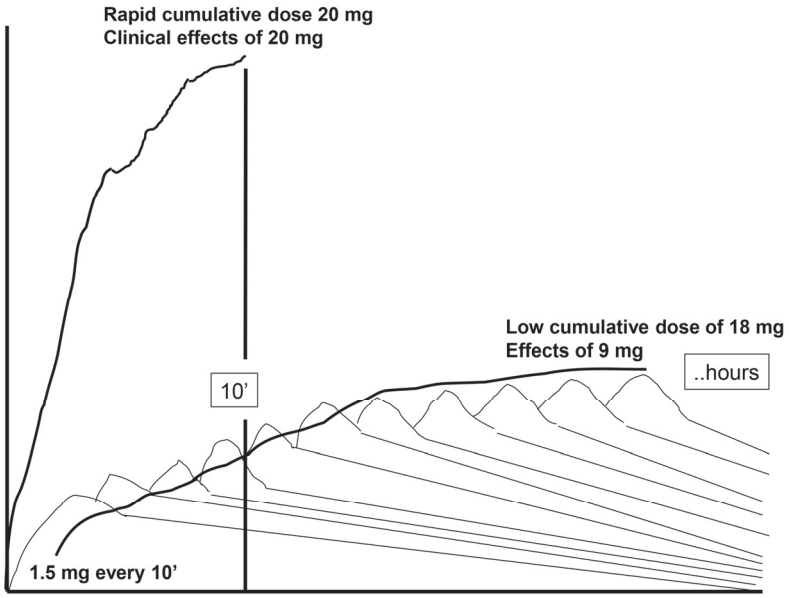

Fig 1. Simulated curves of morphine concentrations with rapid boluses and small cumulative doses

A more intensive approach was proposed. This was commensurate with the circumstances of severe distress of a patient in a painful situation out of control for a long time (30). Intravenous boluses of morphine in doses proportional to the previous opioid consumption (that is the individual level of tolerance) are administered in patients with severe pain intensity (> 7/10 on a numerical scale) until the patient begins to experience a significant improvement, for examle a decrease of 30% in pain intensity. The effective cumulative dose, generally administered in 10-15 minutes, is considered effective for the duration of about four hours. Then, the need for the following twenty-four hours is calculated. The daily dose can be converted to the oral route once analgesic stabilization is achieved, using a traditional oral-intravenous conversion ratio of 3:1. In patients who have resorted to high doses of morphine, or very frail older people, a more conservative conversion, for example 2:1, is used. The oral dose is recalculated from day to day, according to the clinical performance and any requests required. Once a certain stabilization has been reached, the dose for breakthrough pain can be converted to the oral or transmucosal route to facilitate the use at home.

- Patient receiving 100 mg of oral morphine equivalents with severe pain (8/10)
- Dose titration 10 mg of intravenous morphine (expected duration 4 hours)
- Calculated daily dose 60 mg/day (10 mg x 6)
- Conversion to oral morphine: 180 mg (ratio 1:3)
- Conversion to oral morphine in frail patients: 120mg (ratio 2:1)
- Intravenous dose for breakthrough pain: 10 mg (eventually to be converted after stabilization to oral morphine 30 mg

Table 1. Example of rapid dose titration with intravenous morphine.

It is important to consider that patients with pain of high intensity experience psychological distress conditions that can confound the clinical picture. That is, they tend to overexpress their pain by inducing the physician to overestimate the intensity of pain and therefore to administer higher doses, as described in this clinical case (see chapter 10).

A 67-year-old man who had undergone cystectomy and subsequently had been treated with radiotherapy and chemotherapy for a bladder cancer was admitted to the oncology department. Imaging studies demonstrated an invasion of the presacral and paravertebral structures with compression of the sacral and rectal nerves. Pain of high intensity (10/10 on a numerical scale) had been treated unsuccessfully with tramadol and subsequently with oral morphine inconstantly for a few weeks. After palliative care consultation, an opioid titration was initiated in the oncological ward. An effective dose of 40 mg of intravenous morphine was reached. The patient finally relaxed and felt strongly satisfied after some weeks of uncontrolled pain. The dose, considered effective for about 4 hours, was recalculated for the following 24 hours (40 mg x 6 = 240 mg) and converted orally with a prudent ratio (240 mg x 2, rounding 500 mg). The conversion performed was prudent (oral intravenous ratio 1:2, instead of 1:3) in relation to the relatively high dose administered and the setting of an oncological ward, where monitoring is at a lower level. The same 40 mg of intravenous morphine were prescribed as needed for breakthrough pain. The next day, the patient was strongly disappointed because the dose as needed administered was only 10 mg, leaving him dissatisfied and particularly angry with the nursing and medical staff of the oncology ward. A dose titration with intravenous morphine was restarted until reaching 150 mg to obtain an excellent response, without side effects. The dose was converted for the subsequent

24 hours, but maintaining the intravenous route, given the poor stability of the clinical situation (150 mg x 6 = 900 mg/day). The next day the patient appeared very sleepy, confused, with no pain. MDAS was 13 (see chapter on cognitive disturbances, 21b). The infusion rate was decreased to 600 mg/day and subsequently to 300 mg/day with partial improvement in cognitive status after 24 hours (MDAS 11). The infusion was further slowed down to 75 mg/day. In the complete absence of pain and still some drowsiness (MDAS 9), morphine was substituted with methadone 30 mg/day (75 mg/day of intravenous morphine = 150 mg of oral morphine with a ratio of 1:2, converted to 30 mg/day of oral methadone (conversion 1:5), divided into three daily doses, 10 mg x 3. The central side effects disappeared (MDAS 6), and the patient was discharged with well-controlled pain at home with a final dose of methadone of 21 mg/day.

This case underlines how an undertreated patient develops an aggressive attitude and how a state of distress is able to increase the request of analgesics, apparently without initial problems. With the loss of the triggering condition, once the pain was controlled, the anxious-aggressive state disappeared. Paradoxically, opioid requests decreased and a state of toxicity was observed, due to relative overdosage. The toxicity recovered by the reducing of the intravenous doses of morphine and finally the substituting of morphine with methadone. If the pain would have been treated continuously, in the absence of strong stress and strong hostility, the effective dosage of opioids would also initially have been much lower. Thus, psychological distress may induce overexpression of pain (chapter 10).

Under-treatment of pain can result in a nocebo effect, a concept opposed to placebo, that is able to increase nociception through complex pathophysiological mechanisms. This case underlines how intravenous titration in emergency situations with relatively high dosages requires great accuracy and experience in a specialized environment.

The same conditions of distress are often sniffed out thanks to a multidimensional symptom evaluation. Patients with delirium can overexpress their pain and, paradoxically, the administration of opioid subtracting doses can aggravate the confusional state and induce a very dangerous vicious circle. The identification of a delirium status by the common means of evaluation (see chapter 23b) allows timely treatment and minimizes opioid involvement (see figure 2).

A 75-year-old patient with prostate cancer and multiple diffused metastases was admitted for generalized high-intensity pain. He had been

treated at home with increases in the dose of opioids up to 240 mg of oral morphine, unsuccessfully. Upon admission, the patient was subjected to a multidimensional evaluation. The patient presented a "dark" ESAS picture (see figure 2), but above all exhibited clearly elevated MDAS (16/30) values that denoted a state of delirium. Morphine was substituted with low doses of methadone, 21 mg/day, haloperidol 7.5 mg/day was started, and diuresis was forced by hydration to promote the elimination of morphine metabolites. The overall improvement was evident already after 24 hours and continued in the following days. The methadone dose was progressively decreased to 12 mg/day

This case underlines the need for a wider assessment in a patient with apparent uncontrolled pain. In this case a sequence of increases in the dose of morphine had the effect of eliciting or worsening a state of delirium, resulting in overexpression of the painful intensity, in a vicious circle between cause and effect. The administration of haloperidol, by reducing the state of delirium, also allowed indirect control of the expression of pain, allowing a progressive reduction of opioid dosage. In this case it was preferred to switch to methadone to minimize opioid neurotoxicity. The global improvement was evident after 24 hours and continued in the following days with further decreases in methadone dosage down to 12 mg/day.

Dose titration of opioids is a process that requires a lot of circumspection and therefore a special attention to detail. Morphine is a very flexible drug for the various modes and dosages available for administration, and can be a reference for the equivalent doses of other drugs. Beyond the modality and the choice of the drug for titration, dictated by clinical circumstances, the administration of drugs as needed is essential for an appropriate titration, as it is impossible to know a priori the dosage necessary to control the pain. Close clinical contact is essential in the first days to optimize the intervention, to prevent side effects, and to shorten the time of uncontrolled pain, by modifying the dosages appropriately. Increments of 33-50% are generally acceptable, taking into account that the parenteral route can accelerate the achievement of an optimal clinical situation in patients who are more resistant or have undergone a period of under-treatment that makes the required final dosage even more unpredictable.

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CHAPTER NINETEEN B

ADVERSE EFFECTS RELATED TO OPIOID THERAPY

The binding of opioids with their receptors produces analgesia and a number of other undesirable effects. The balance between analgesia and the side effects defines the opioid response (see chapter 19c): increasing doses of opioids may produce analgesia up to a level where adverse effects will appear that limit further dose escalation (1). So the ceiling effect of opioids is not represented by the dosage, but rather by the entirely individual propensity to develop side effects. Side effects negatively affect quality of life, increase morbidity, and may cause patients to discontinue opioid therapy. Cultural attitudes towards the opioid-adverse effects may be a barrier for the use of opioids (2) and represent an important limitation for a correct analgesic treatment (3). Some side effects, with the exception of constipation, tend to shrink spontaneously over time in a good proportion of patients. In many patients there is a physiological neuronal adaptation, such as tolerance. Other side effects, however, tend to consolidate over time, such as those concerning the endocrine sphere and the immune function.

In general, all the phases in which the dose is initiated or increased are the most critical, while stalemates should not cause any particular damage unless there are clinical and metabolic changes that result in an increase in the effect of the same dose (see chapter 14). The dose of opioids in general is not intended as a determining factor in chronic treatments, but represents a potential risk for the development of toxicity, especially of neuro-excitatory nature, in successive phases.

Data on the incidence of side effects are difficult to interpret. Solid data on the side effects of opioids in cancer patients are unlikely for a series of coexisting problems related to the disease and the administration of a myriad of drugs with similar effects, often inseparable from the effects induced by opioids, or the simultaneous administration of symptomatic drugs. Paradoxically, it has been observed that an effective opioid dose titration may be able to limit some effects erroneously

attributed to opioids because the pain itself may be accompanied by satellite symptoms that concomitantly decrease in intensity with the reduction of pain (4).

Clinical aspects in cancer patients

With a good approximation, the incidence of side effects related to opioids is 40-70% for constipation, 10-80% for myoclonus, 20-60% for sedation, 15-20% for nausea, and 2-10% for itching, with the wideness of these ranges resulting from by the lack of homogeneity of existing studies, due to the presence of elements of confusion, such as the stage and progression of the disease, comorbidities, drugs, subjective variability, the period of administration, the doses of drugs, and variable symptom assessment (5). There is not much literature data on which disorders are more important than others for a cancer patient. The most significant effects appear to be constipation, nausea and vomiting, urinary retention, pruritus, hallucinations or confusion, respiratory depression, sedation, vertigo, myoclonus, and dysphoria (6).

In a longitudinal, and therefore realistic study on a sample of cancer patients in which morphine was used for 4 weeks, the most frequent symptoms were represented by dry mouth (95%, moderate-severe intensity, for a duration of 20% in the study), sedation, and constipation (88%, of moderate-severe intensity, but with a low prevalence of the period), while nausea was reported by about half of the sample. Myoclonus was unexpectedly very common (83%), although not severe and persistent. While a continuing same dose of morphine did not have a particular impact on the side effects, dosage changes were associated with constipation, dysphoria, myoclonus, nausea, and sedation (7).

Patients titrated with an initial dose of oral morphine of 60 mg/day and with a standardized dose increase schedule, with an average dose increase of about 50% over about two days, exhibited mostly nausea and constipation, while in a quarter of patients titration had to be stopped due to the appearance of sedation (8). Therefore, the development of side effects may slow the opioid dose escalation. The subsequent development of tolerance to most of the side effects allows the dosage to be increased in the subsequent days, when the patient has stabilized at that determined dose and it is possible to proceed to a new increase.

In some cases toxicity is not synchronous with the increase of the dosage, or it can even appear in conditions of apparent stability for some modifications of the clinical state. Some pharmacokinetic changes due to recent clinical changes may accentuate the likelihood of side effects. For

example, an accumulation of hydrophilic metabolites (see chapter 14) in an old patient with severe dehydration, and pre-renal insufficiency may produce delayed toxicity, although clear relationships between the concentration of metabolites, parent molecules, and the appearance of side effects have never been demonstrated (9-11). In these cases, the possible toxicity may persist for several days, even after stopping the treatment with morphine due to the persistence of active concentrations of M6G. Increasing the dose of a drug such as methadone may cause delayed toxicity as a result of a slow accumulation, typical of its pharmacokinetics, or following a concomitant use of a drug that limits its metabolism and therefore increases its effect (see chapter 14).

There are data, not definitive, for the benefit of the parenteral and transdermal route over the oral route with regard to the frequency of gastrointestinal symptoms, such as nausea and vomiting, and constipation (12). It is not clear whether this is related to the characteristics of the route or the medication used (5). Myoclonus was more likely to occur with morphine administered orally than parenterally (13).

General lines of treatment

In general, the treatment of opioid-induced side effects involves various modalities whose relative efficacies have never been determined in appropriate studies (14). There are some therapeutic options to decrease the burden of opioid-induced adverse effects (table 1).

a) opioid dose reduction
b) symptomatic treatment of side effects
c) opioid switching
d) substitution of the route of administration

Table 1. Modalities to improve opioid response when adverse effects develop

a) A reduction of opioid dosage allows the reduction of the intensity of side effects, but at the same time leads to a reduction of analgesia. This situation requires a synergistic analgesic treatment that compensates for the reduced analgesic activity after opioid dose reduction. By chance, one can test responsiveness to non-opioid drugs, such as anti-inflammatories or other adjuvants, such as antidepressants or anticonvulsants, which can provide an advantage in certain clinical situations associated with a particular mechanism of the pain syndrome. The overall response is

somewhat variable and unpredictable, and in itself introduces a new source of possible side effects and a greater likelihood of drug interactions. Combined treatments with regard to the disease, such as radiotherapy, surgery, chemotherapy, or certain analgesic blocks, can find indications in particular clinical conditions, even if in terms of evidence there are no data in favor of these techniques, given also the lack of uniformity of the approaches and above all of the evaluation.

b) The use of drugs that can prevent or reduce the side effects of opioids is definitely the most commonly used treatment. The available data, however, do not present scientific solidity and are based on anecdotal experiences. Again, this approach includes the introduction of a new drug, and therefore a new variable capable of producing side effects per se, as well as increasing the risk of interactions.

c) Opioid substitution is increasingly used in the clinical setting, on the basis of a series of positive experiences and a greater knowledge of this pharmacologic technique that requires some confidence in the handling of opioid doses (see chapter 19d). Though opioid substitution has the practical advantage of minimizing the side effects or enhancing analgesia, the results are unpredictable and often it is necessary to resort to multiple substitutions before reaching the optimal result.

d) The change of route has been invariably reported to improve the opioid response in some clinical conditions, particularly in the presence of gastrointestinal side effects. However, the data cannot be considered definitive (see chapter 17).

Although a differential diagnosis is often complex, iatrogenic causes such as the use of drugs or possible interactions, or the presence of clinical situations (cerebral organic alterations, hypoxia, intestinal obstruction) or confounding biochemical abnormalities (dehydration, hypercalcemia) should always be taken into consideration. Correction of an identifiable reversible cause can often be resolutive with respect to a series of effects erroneously attributed to opioids.

Some factors must be taken into account when considering the different options available in the treatment of opioid-induced side effects (table 2).

- Convenience: treatments must be simplified as much as possible with a low number of drugs, especially in an unprotected environment.
- Availability: options often depend on the availability of drugs, varying from country to country.
- Cost: some symptomatic drugs can be expensive, even more than analgesic treatment.
- Familiarity: the choice should rely on the drugs with which the practitioner has greater confidence, even if an additional effort is often necessary to familiarize himself with all the possible options, in particular with the opioid conversion ratios.
- Patient's preference: it is fundamental to ask and discuss the possible options and to choose also according to the abilities, the setting of care, and the wishes of the patient.

Table 2. Practical factors determining the choice of treatment

Adverse effect	*General treatment*
Nausea and vomiting	Antiemetics, opioid switching/route
Pruritus	Anti-histamines, opioid antagonists, 5HT3antagonists
Drowsiness	Drug re-evaluation, psychostimulants, opioid switching
Myoclonus	Muscle relaxants, opioid switching
Delirium	Haloperidol, opioid switching
Respiratory depression	Discontinuation, opioid antagonists
Constipation	Laxatives, peripheral opioid-antagonists
Sweating	Anticholinergics
Urinary retention	Anticholinergics
Hyperalgesia	Opioid switching, adjuvants
Hypogonadism	Hormone replacement

Table 3. General lines of treatment of opioids-induced adverse effects.

Gastrointestinal effects

Due to its complex and multifactorial nature, the pathophysiology of the main gastrointestinal effects induced by opioids, such as nausea and vomiting, and constipation, will be dealt with in more detail in specific chapters. Opioids exert an emetogenic effect for a series of multiple

mechanisms on the trigger area, stimulating dopaminergic receptors, and on other areas, such as the vestibular and visceral, through the activation of cholinergic, histaminergic, and serotonergic receptors. They also induce a gastroparesis and slow the intestinal transit. These effects generally appear early, but tend to fade over time due to the appearance of tolerance (7). In fact, there are numerous causes of nausea and vomiting, often more decisive and frequent than the use of opioids. The temporary use of antiemetic drugs with a different action is the consequential treatment, other than a spontaneous resolution due to the development of tolerance (see chapter 22c).

Unlike most of the side effects of opioids, constipation tends to remain constant along the course with opioid treatment. Although there is no correlation between opioid doses, the extent of constipation, and laxative doses, there is a high likelihood that patients receiving high doses of opioids will undergo constipation. The genesis of constipation is multifactorial in the cancer patient, but the use of opioids is recognized as one of the main causes. The phenomenon is widespread in cancer patients, and even more so in those receiving opioids. Patients' condition, lack of mobilization, state of dehydration, and use of drugs, such as antidepressants, antacids, anticholinergics, and diuretics, accentuate this phenomenon. Therefore constipation is a significant and persistent problem to face along the course of disease (see chapter 22b).

Opioids cause constipation by binding specific enteric receptors. The activation of intestinal μ-receptors determines the relaxation of the internal smooth longitudinal fibers for the reduction of acetylcholine release. Opioids inhibit the tonic inhibitory activity exerted by neurotransmitters as vasointestinal peptide (VIP) on the circular musculature, causing spastic activity, particularly at the level of the sphincters or stimulating non-propulsive motility at the level of the ileum and the colon. Thus, they contribute to increasing the intestinal transit time. In addition, opioids have a direct role in reducing intestinal secretions by inhibition of the VIP, the main secretagogue substance. The increased solidification of feces may contribute to the appearance of nausea, vomiting, and abdominal pain, paradoxically induced by opioids. Finally, opioids can reduce the effects of defecation by a central and spinal effect, and produce an increased capacity at the level of the rectal ampoule. The use of laxatives is widespread in association with opioids, particularly in cancer pain. In addition there are molecules that, for pharmacokinetic reasons, tend to have a reduced intestinal disposition for their lipophilic properties, such as methadone, due to the lower opioid activity, tapentadol for the limited opioid receptor activity, and fentanyl and buprenorphine, also probably for

the type of administration. Finally, the combination of opioids with antagonists, which determine their effect exclusively at the peripheral-intestinal level, may limit the constipating effect of opioids (see chapter 22b)

Drowsiness

Opioids commonly induce sleepiness and a reduction in cognitive function. Reducing the acquisition, processing, storage, and recall of brain information leads to lower attention, disorientation, agitation, hallucinations, and delirium, phenomena that have a significant effect on the quality of life of patients and family members. These changes in mental state are quite complex and difficult to measure in the diversity of clinical presentation, especially in relation to the evolution of the disease, possible co-morbidities, active drugs on the nervous system used simultaneously, and biochemical and metabolic modifications.

The incidence of such disorders is high in cancer patients, although variable in the literature, with peaks of 90% in the last days of life (15).

In general, drowsiness spontaneously decreases within a few days of starting opioid therapy, persisting at levels considered acceptable, or recurring during the steps of dose increase. In other cases, it affects the continuation of treatment.

The evidence of the effect of opioids on psychomotor performance is quite controversial. It is believed that in a patient with a good performance status, the changes are not relevant if the dosage of opioids remains constant, unlike patients who undergo major psychomotor abnormalities as a result of recent dose increases. Indeed, it has been observed that neuropsychological performance is more affected by the presence of uncontrolled pain or poor performance status than by the administration of oral opioids (16). In the advanced stages of the disease there are often other factors that can worsen the cognitive activity. The ability to drive is a typical example. Simulation tests have shown that patients treated with stable doses of opioids maintain a similar reactivity compared to patients rehabilitated to the license after a vascular episode. Beyond these potentially reassuring data on the use of opioids and the ability to drive motor vehicles, prudence seems to be required, exactly as for all other central nervous system drugs, more easily accessible and unregulated, which act on the nervous system, especially after recent dose increases (17).

Paradoxically, this symptom has been reported more frequently in young people, probably due to a greater intolerance to cognitive

limitations produced by opioids in this population (7). Often, somnolence is dependent on the overlapping effects of different drugs with a pharmacodynamic interaction, on the progression of the disease, and on the worsening nutritional status. Thus, concomitant diseases such as dementia, metabolic encephalopathy, brain metastases, or the use of some centrally acting drugs contribute to an increasing of the opioid sedative effect.

It has been reported that the use of immediate-release morphine, used in patients receiving slow-release morphine, produces a transient decrease in the anterograde and retrograde memory (18), although it should be emphasized that the administration occurred in the absence of breakthrough pain. The persistent sedation intensity beyond the titration or dose increase phase can be reduced by decreasing the dose, even if this often coincides with a worsening of pain intensity. In some cases, it is necessary to substitute the opioid to maintain the same degree of analgesia with lessened side effects, or to change the route of administration in the case of morphine, if metabolite accumulation is suspected to play a role in the clinical situation.

The use of psychostimulant drugs may increase the therapeutic window by limiting the level of drowsiness while the opioid dosage remains unchanged to maintain a constant analgesia. Some of these substances, which generally act on the activating reticular system, would also have an analgesic effect. The main side effects are represented by insomnia, agitation, and weight loss.

Methylphenidate is a nervous system stimulant approved for the treatment of narcolepsy. Although the mechanism of action is not well known, it appears to block dopamine reuptake by binding a transporter at the level of the presynaptic membrane, thus increasing the extracellular dopamine levels, particularly at the striatum nucleus. To a lesser extent the reuptake of serotonin and noradrenaline is also limited. Absorption is quite good by mouth. The doses are 5-10 mg, for a maximum daily dosage of 60 mg, preferentially to be administered during daytime hours.

In cancer patients it is used for the control of central opioid toxicity, cognitive disorders, and fatigue. For the control of opioid-induced somnolence, data are quite interesting, even if there are still no convincing evidence on a large scale. Approximately 10% of patients experience cardiovascular (tachycardia, tachyarrhythmia), central (insomnia, dyskinesia, tremor), gastrointestinal (xerostomia, anorexia, abdominal pain), and cutaneous (urticarial reactions) side effects (19).

Modafinil is a drug used for narcolepsy, acting with different mechanisms than those of amphetamine. It seems to act on various

systems, such as catecholaminergic, serotonergic, glutaminergic, and histaminergic ones. Modafinil, in doses of 100-200 mg, improves memory and other cognitive processes dependent on the frontal cortex. Tolerability seems good enough (19). It can be used during titration or in support of a substitution of opioids when cognitive dysfunction is the leading symptom (20).

Pemoline is a central stimulant with minimal sympathomimetic activity. The mechanisms and the site of action are not well determined. It probably exerts an inhibitory effect on the synaptic reabsorption of dopamine. Pemoline, like methylphenidate, can be absorbed from the oral mucosa. It is partially metabolized in the liver and eliminated in the urine. It is given as a single dose in the morning (37.5 mg) to be increased if necessary to reach the effect up to 112.5 mg, with a very gradual expected effect up to 3-4 weeks.

The donepezil, an oral acetylcholinesterase inhibitor used in Alzheimer's disease, has been reported to be effective in improving brain function without affecting opioid analgesia in 5 mg doses (6). A certain tendency towards tolerance development has been observed. Psychostimulants should not be prescribed for patients with psychiatric problems, or with hyperactive delirium or hallucinations.

Finally, in very select cases, in which none of the previous procedures have been effective, the spinal route for providing analgesia with lower doses of opioids should be considered, if the expected survival and the clinical conditions allow it (see chapter 20).

Sleep disorders

Sleep disorders are quite frequent in cancer patients. As sleep and waking are regulated by many neurotransmitters, a variety of drugs, such as opioids, can potentially interfere with sleep. Although the mechanism is unclear, it has been observed that morphine reduces REM sleep, probably by inhibiting the release of acetylcholine at the level of reticular formation (21). Respiratory disorders prevail during the non-REM phase, contrary to what is commonly observed in obstructive sleep apnea. In a polysomnographic study in patients on chronic opioid treatment, the apnea-hypopnea index was abnormal in 75% of cases, with a significant relationship with methadone and benzodiazepine alone, but not with other opioids (22).

It remains difficult to differentiate the role of the alteration of sleep by the disease and the drugs prescribed together with the opioids. On the

other hand, it is quite clear that the presence of uncontrolled pain is one of the most frequent causes of altered sleep (15)

Cognitive function

The worsening of cognitive function is often associated with a confusional state, psychomotor agitation, and the appearance of hallucinations and myoclonus. The causes of delirium are multiple (see chapter 21b), but one of the best known reasons is the use of opioids in increasing doses, responsible for precipitating factors in a large number of cases (15). The presence of renal failure, pre-existing cognitive disturbances, the use of drugs acting on the central nervous system, or a state of profound dehydration greatly increase the risk of opioid-induced delirium. This behavior is presumably due to an imbalance between the cholinergic and dopaminergic system, due to the anticholinergic effects induced by morphine. Hallucinations may be due to the alteration of cholinergic control over various brain areas.

As a general rule, treatment should include the removal of any responsible or aggravating factors, such as dehydration, and a reduction in opioid dosage. The standard treatment involves the use of antipsychotic drugs such as haloperidol, which helps to balance the dopaminergic–cholinergic axis for its antidopaminergic action (6). Often it is necessary to completely replace the opioid, without neglecting good hydration, often previously incomplete, but which would however favor the eventual elimination of toxic substances present and normalize any biochemical parameters. Cholinergic drugs, such as cholinesterase inhibitors, donepezil, or physostigmine, have been proposed although more experience is needed.

Myoclonus

Myoclonus is a sudden, jerky, uncontrolled movement, generally limited to a few muscle groups, especially the limbs. The frequency is very variable in the literature, with a higher probability with high doses of opioids, albeit unpredictably (23). Meperidine is associated with the highest probability of developing myoclonus, due to the active metabolite, normeperidine, which has a neurotoxic potential. The risk seems higher with oral morphine compared to parenteral morphine, underlining the possible role of metabolites (13), as well as in the presence of spinal injuries (15). The concomitant use of other drugs, antidepressants, neuroleptics, and antiemetics increases the risk. Various mechanisms have

been postulated, including the presence of toxic metabolisms such as M3G and M6G, the inhibition of glycine synthesis with the loss of inhibition by this transmitter, the activation of the NMDA neuro-excitation system, and dopaminergic antagonism at the basal ganglia level.

Myoclonus is often nocturnal initially. Opioid dose reduction and the use of muscle relaxants such as baclofen, benzodiazepines, or gabapentin have been used occasionally, although there are no sufficiently definitive studies. Generally, however, the neuro-excitatory state responds better to opioid switching, discontinuing the possible offending drug.

Pruritus

This is a symptom that is observed more specifically with the administration of spinal opioids. Although not dangerous, pruritus is largely bothersome and unpleasant. Some data report a 2-10% frequency in patients receiving morphine, which is more strongly involved than other opioids for histamine release (24). The concomitant use of other drugs, antidepressants, neuroleptics, and antiemetics increases the risk.

The mechanism has not been clearly elucidated, but it appears to be predominantly mediated by μ-receptor activation, although a receptor involvement has been more recently demonstrated. The greater distribution in the trigeminal area has been explained by the high opioid-receptor concentration in the trigeminal nucleus. The involvement of dopaminergic and serotonergic receptors, the release of prostaglandins and histamine, and antagonism on GABA receptors and glycine have frequently been called into question.

There are no specific data on the treatment. Therefore, the indications remain empirical and based on the consequential use of antihistamines, such as difenyldramine, hydroxyzine, and promethazine, even if the direct antihistamine effect does not seem to be confirmed, the sedative effect probably prevailing. Many treatments are effective for acute opioid administration, as in the case of propofol. Data on the use of ondansetron, an antagonist of serotonergic 5-HT3 receptors, are contradictory. Also, dopamine-agonist drugs such as droperidol and alizapride have been used successfully. The use of μ-receptor antagonists or agonist-antagonists, such as nalbuphine, is quite effective, but does not find an indication in the treatment of chronic opioid cancer pain, due to the possible reversibility of analgesia (25).

Dry mouth

Dry mouth is one of the symptoms most frequently associated with the use of opioids, particularly with morphine, for persistence and intensity (7, 26). The use of pilocarpine in low doses is generally effective and fairly tolerated (27). The most likely side effects are those of cholinergic type, such as sweating and diarrhea.

Many humectants are commercially available, although they have a limited duration of effect and require very frequent use. Anecdotally, the use of substances that increase salivation such as pineapple or lemon juice is often reported.

Dysuria

This is a poorly studied symptom with opioids administered systemically. It is often specific to the route of spinal administration, for the phenomena of dissolution between the activity of the bladder muscles and the sphincter. In a longitudinal analysis, this symptom presented a not inconsiderable prevalence of 23%, rarely reported in other studies (7, 28). Because of the complex mechanism of micturition, many drugs can interact with the micturition pathway with different modalities. Urinary retention has been described with the use of drugs with anticholinergic activity (e.g. antipsychotic drugs, antidepressant agents, and anticholinergic respiratory agents), opioids, anesthetics, alpha-adrenoceptor agonists, benzodiazepines, NSAIDs, detrusor relaxants and calcium channel antagonists. Elderly patients are at higher risk because of existing local co-morbidities and the use of other concomitant medication reinforcing the impairing effect on micturition. Drug-induced urinary retention is generally treated by urinary catheterization, especially if acute, in combination with discontinuation or a reduction in dose of the causal drug. Alternately, an alpha-antagonist may be beneficial.

Respiratory depression

This side effect raises major concerns because this is a severe complication, possibly leading to death. As with other effects, tolerance develops rapidly. Breathing is controlled by a chemoreceptor mechanism in the ventral mid-high area and by carotid chemoreceptors, sensitive to the concentration of carbon dioxide (CO2). A CO2 increase leads to a stimulation of the respiratory muscles to breathe more deeply and quickly. In the presence of adaptation to higher levels of CO2, such as in chronic

respiratory failure, oxygen concentration becomes determinant in regulating breathing. In the presence of substances that depress the medullary center, response to CO2 is reduced and consequently a reduced muscle response is observed. Opioids produce a depression of the respiratory center and a reduction of sensitivity to CO2, with a decrease of frequency and respiratory volume. In the presence of pain, however, this effect seems to be compensated by the pain intensity (29), as pain would be a natural antidote to opioid overdose. An accurate opioid dose titration is therefore risk-free, since the plasma levels necessary to obtain analgesia are always lower than the levels able to induce a respiratory depression.

Some conditions may be a risk, such as chronic-obstructive bronchopathies, some muscular and neurological degenerative diseases, and obesity, as well as older people having severe metabolic problems that can lead to an artificial increase in dosage due to problematic metabolic elimination. Respiratory depression is proportional to the opioid dose (30).

The appearance of tolerance and especially the presence of pain provide important protection against this effect. Often the appearance of respiratory failure due to heart failure, pulmonary embolism, or bronchopneumonia, or the deterioration of brain function with respiratory center involvement, is attributed to the use of opioids. In other cases the concomitant use of other drugs may increase the level of sedation up to a level determining respiratory depression. In most cases an overdose, usually accidental, of opioids, produces respiratory depression. The use of naloxone, an opioid-antagonist, should be reserved only for patients with a respiratory rate of less than eight acts per minute, to avoid inducing inappropriate withdrawal symptoms with exacerbation of the painful condition. In any case, doses should be slowly titrated until increasing the respiratory rate. In most cases a dose reduction or temporary suspension slowly allows a spontaneous resolution.

Addiction

Addiction is a neurobiological disease produced by chronic exposure to a drug that can produce it and is characterized by the loss of control of its use (31). Epidemiological studies in humans, experimental studies in animals, and imaging studies have shed light on the mechanisms of addiction production. In particular, the repeated use of these substances determines neuroadaptation processes that profoundly alter brain functions. This adaptation depends on a series of genetic and psychosocial factors, and some others that are specific to the type of drug used (32). Unlike physical dependence and tolerance, depending on a drug, addiction

means a compulsive behavior that has as its object the obtaining of the substance. The criteria for defining dependence on psychoactive substances, according to the DSM-IV, are listed in table 4.

- Tolerance to the effects of the substance
- Physical dependence (withdrawal abstinence symptoms)
- Dosages used above those prescribed
- Unsuccessful attempts to reduce doses
- Reduction of social and employment activities
- Continued use despite the social and occupational problems, and notices in this sense

Table 4. Criteria for defining dependence on psychoactive substances, according to the DSM-IV

Opioids exert at this level a double action, direct and indirect, inducing a series of neurochemical adaptation phenomena. The negative effects of reinforcement produced by the suspension of the drug (withdrawal anhedonia), are the most important stimulus for compulsive behaviors that motivate the need to seek the substance. The activation of cyclic adenosine monophosphate (AMPc) in the locus ceruleus, the most important regulating center for noradrenergic tone, induced by the repeated administration of opioids, leads to the activation of enzymes for the transcription of genes and represents the central mechanism for the appearance of physical dependency, that is the appearance of physical symptoms following abrupt withdrawal of opioid administration, or the use of an opioid-antagonist. These effects are initially of short duration, are resolved at the end of the crisis, and are distinguished from compulsive behaviors that persist even after the exhaustion of the crisis. Once addiction develops, these brain alterations are reinforced not only by the continuous or intermittent use of the opioid, but indirectly by the consequent behaviors and by the circumstances associated with obtaining the drug, which stand out in the memory, as in all the conditioned responses. They are difficult to eradicate even after the suspension of use.

Structures involved in the processes of memory, conditioning, and learning are involved, such as the amygdala, hippocampus, and cerebral cortex. Dependency is thought to occur through the dysregulation of the reinforcing mechanisms reaching a new equilibrium, defined as allostasis, in which the pleasant effect of the drug decreases and the incentive effects increase, leading to a compulsive attitude (33).

While initially dependency was explained as a kind of development of tolerance that requires further increasing doses to meet the expected needs, the mechanisms of reinforcement and neuroadaptation allow the explanation of the frequent relapses. Neuroadaptation occurs through the reorganization of the nervous circuits with plastic modifications at the synaptic level, alterations in intrinsic excitability, or structural modifications. The longer the abuse is maintained, the more irreversible the adaptation will be. These adaptations are therefore not only linked to the use of an additive substance but to the complex interaction between the effects of the drug and some individual favoring elements: the character vulnerability, probably genetically predetermined, and environmental and social factors. In the case of opioids, the appearance of unpleasant effects, both physical (tachycardia, agitation, hyperalgesia) and psychological (anhedonia), may persist insidiously and intermittently already during the prolonged use in the form of minicrisis of abstinence.

In recent years, a role has been attributed to the activation of glia by opioids, with a stimulation of the so-called toll-like receptors (TLR), involved not only in painful processes, but also in the appearance and maintenance of dependence for complex interactions concerning the production of interleukins (see chapters 7 and 8) (34). The behavioral response is quite individualized: some subjects positively tolerate these effects, others suspend the use of the substance due to the unpleasantness of the situation, and others require the same substance in an attempt to mitigate these effects. These last subjects are at greatest risk: if their needs are not structured in the context of an adequate treatment, they develop an insidious behavior known as addiction abuse.

In cancer patients there is a certain cultural reluctance on the part of the medical specialist to consider the risk of the development of addiction, since this is a problem that has long criminalized and limited the appropriate use of opioids, and that seems to be less important in this context. The underestimation of these aspects conveys the inherent risk of confusing terminology and addictive symptoms. For example, a patient being treated with opioids whose pain is not controlled and who requires dose increases is not a dependent patient, as he belongs to the category of patients who develop tolerance or in whom pain commonly reappears during disease progression. The pathological behaviors commonly attributable to opioid abuse could equally be signs reported by undertreated patients (table 5).

- The patient focuses on the use of opioids, diverting attention from the pain syndrome - The patient requires dosage increases in the absence of clear signs of disease evolution, even outside of scheduled visits - The patient has problems with supplying (lost, stolen, etc.) - The patient gets supplies from other sources (first aid, other doctors, illegal sources)

Table 5. Criteria for establishing a "problematic" use of opioids

The percentage of opioid abuse in patients with chronic non-cancer pain is very high, from the first published reports (5%) to the present day (70%) (35), with a figure of 7% for cancer patients, although the diagnostic criteria are not well understood. In cancer patients, chemical coping was diagnosed in 18% of outpatients with cancer. Patients with cancer are also at a risk for aberrant use of prescription drugs if they have a preexisting issue with drug and substance abuse (36). Thus, clinicians are faced with the challenge of helping patients who need to use opioids safely while minimizing opioid misuse and addiction.

Clinical experience has taught that appropriate monitoring minimizes the development of aberrant behaviors, using few essential principles. In the treatment of non-cancer pain the decision to start opioid treatment should be carefully considered, balancing the possible benefits with the risks of a long and complex pharmacological commitment, and assessing the need for a close collaboration on the part of the patient regarding the problems of prolonged use of opioids. This requires frequent re-evaluations. Cancer patients have a very different natural history. In Mediterranean countries, many patients are already opposed due to cultural prejudice to the use of opioids, and physicians tend instead to persuade the patient of the need for their use, rather than to present their risks. Naturally, all the pillars used in non-cancer chronic pain – the counting of the pills, the doctor-patient contract, urine analysis, and all the means commonly used for the prevention of abuse – are out of place in this context. The Screener and Opioid Assessment for Patients with Pain – Revised (SOAPP-R) is a self-report questionnaire designed to predict aberrant medication-related behaviors among persons with chronic pain. This measure was developed to improve a clinician's ability to assess a patient's risk for opioid misuse. Short forms from the 24-item SOAPP-R total score enhanced the efficiency of this tool (35, 36).

There are currently no well-defined strategies to manage cancer patients on chronic opioid therapy who develop aberrant opioid-related

behaviors. A standardized strategy based on education and comprehensive assessment allowed timely patient identification, management, or referral to the appropriate specialist teams (37).

While the increased use of opioids for clinical purposes has over time corresponded to an increase in abuse due to unavoidable neurological adaptations, with the development of aberrant behaviors in the most vulnerable subjects, opioids remain indispensable in the treatment of severe cancer pain. Rather, the risk of addiction should be considered, recognized, and probably accepted and enrolled in the various clinical issues related to the use of opioids, especially in healed or long-survivor patients.

Physical dependence: this appears after abrupt withdrawal or reduction of the dose, or the administration of an opioid antagonist. Typical symptoms and signs of a withdrawal syndrome are: agitation, irritability, increased sensitivity to pain, nausea, abdominal cramps, myalgia, dysphoria, anxiety, insomnia, sweating, piloerection, tachycardia, diarrhea, hypertension, dilatation of pupils, fever, and rhinorrhea. This is a neurophysiological adaptation consequent to the alterations of the receptor state.

Psychological dependence: this is a maladaptation behavior, characterized by the need to use the drug with a high tendency to relapse, and the loss of control. This is a behavioral and psychological process. It translates into a desire to use the drug, with a compulsive attitude, and is characterized by continuous use despite side effects, an increase in doses, attempts to defraud in the receiving, always looking for more sources of availability, even illegal, and the use of other drugs or substances for abuse. *Pseudoaddiction*: this is a form of iatrogenic syndrome similar to drug addiction, but which develops following an inadequate analgesic treatment. Uncontrolled pain increases the demands and induces an attitude in search of the drug that leads to the suspicion of the physician, who consequently feeds this process, reducing the supply of opioids, further increasing the patient's frustration. *Abuse*: this describes an inappropriate use, outside of therapeutic indications and that causes risks of overdose. It may be associated with dependence.

Table 6. Nomenclature assessing a "problematic" use of opioids.

Immunological and endocrine effects

The correlation between pain and inflammation is well known. Peripheral damage is followed by inflammation associated with the migration of leukocytes and other immune cells. Some substances, such as K +, H +, bradykinin, substance P, prostaglandins, and cytokines, are released locally. Cytokines, by promoting different transcription factors, mediate the synthesis of active substances such as prostaglandin E2 and substance P, and play a significant role in bone marrow sensitization, as demonstrated by experiments performed with specific antibodies in experimental models of neuropathic pain (38). Opioids share some properties of cytokines, the main mediators of the immunologic function, and interact in a complex way. Acute and chronic administration of opioids interferes with immune function through various mechanisms, including an inhibitory effect on antibody and cell responses, on natural killer lymphocytes, on the expression of cytokines, and on phagocytic activity. However, many questions remain open regarding the biological significance of the measurable humoral alterations in relation to acute and chronic administration in the presence of a pain syndrome.

a) Opioids and immunological response

There is evidence that opioid receptors are expressed by cells of the immune system and can regulate these processes through peripheral and central mechanisms. The increased incidence of infections in drug users was initially attributed to poor hygiene or impurities, while recently the illicit use of opioids has been considered as a cofactor for the development of HIV, and prolonged administration linked to increased susceptibility to viral and bacterial infections.

While exogenous opioids generally produce a reduction in the immunological response, endogenous opioids, which perform a physiological function, appear to exert opposite effects. Like cytokines, endogenous opioids are low molecular weight substances, widely distributed in the nervous system where they perform communication, transmission, or signal modulation functions. The effects of exogenous opioids can be mediated centrally and peripherally. The central effect is strongly linked to the endocrine response, involving both the hypothalamic–hypophyseal axis, particularly for chronic administrations, and the vegetative nervous system, especially for acute administration. In the periphery, immune cells can produce endogenous opioids and modulate analgesia and inflammation locally, while exogenous opioids

can modulate the secretion and receptor expression of inflammatory cytokines, creating a bidirectional system in which opioids, immune cells, and their mediators interact dynamically (39).

b) Cytokines and opioids

Cytokines are low molecular weight substances released in response to the presence of antigens, and stimulate various immune and inflammatory cells. Cytokines are usually not stored but are produced as a result of a stimulus in a transitory synthesis following a genetic transcription. A cascade of events from multiple activation can even lead to antagonizing effects in some cases. The binding of a cytokine with its receptor will activate a series of intracellular messengers that generate a transcription for the synthesis of proteins, with a complex regulatory and differentiating function on the immune cells. Some of the common properties of exogenous cytokines and opioids are the production of immune cells at various sites according to pleiotropism (action of a cytokine on different types of cells), or redundancy (action of various cytokines with similar functional effects), depending on the time of administration and the dose of the opioid. As previously mentioned, opioids can alter the function of all types of immunocytes. The peripheral administration of morphine is followed by a rapid and significant increase of the proinflammatory IL6 cytokines, probably through the mediation of the vegetative system, as demonstrated by blocking or adrenalectomy experiments. At the central level, opioids stimulate hypothalamic neurons with an inhibition of NK cells, through an activation of the hypothalamic vegetative system. The glial cells, previously considered simple connective structures of the nervous system, have instead shown a neuroimmunological action and a fundamental role in the mediation between cytokines and opioids. Indeed, opioid receptors have been found in astrocytes. On the other hand, lymphocytes and monocytes are able to express opioid receptors. Local analgesic effects of exogenous opioids are pronounced in inflammatory conditions and are mediated by the presence of peripheral opioid receptors. Chemokines are substances that are structurally similar to cytokines, which regulate the migration of inflammatory cells. Opioids induce a slowing of chemotaxis with a desensitization of chemokine receptors. In contrast, the activation of chemokine receptors produces a desensitization of peripheral opioid receptors. Various studies have shown that morphine induces immunosuppression of NK lymphocytes, with a central and peripheral mechanism. T-cell proliferation is also severely compromised in a dose-dependent manner, regardless of cortisol levels.

Despite numerous experimental evidences oriented towards a central mechanism, the final target of these effects involves peripheral mechanisms, with an increase in the production of nitric oxide (NO) by macrophages (39).

c) Acute administration of opioids and immune response

The acute administration of an opioid agonist results in an immunosuppressive response. Numerous animal studies have demonstrated a suppression by morphine of cell killer activity, cytokine production, and induced lymphocyte proliferation, both by venous and ventricular administration. This reaction is attenuated or prevented by the administration of naloxone (40). These observations suggested an involvement of opioid receptors. The suppressive effect appears to be related to the dose used. Fentanyl also showed similar effects albeit at higher doses (41). Acute effects on immunity have given rise to conflicting and uncertain results. Substantially, the immunological functional measures are negatively influenced, but how much this is reflected in relation to a susceptibility to new antigens, for example of cancer cells, remains to be demonstrated. Furthermore, the responses seem to be conditioned by the type of animal and the timing of the administration of morphine.

The presence of pain represents a further challenge in understanding the complex immunological events attributed to an acute opioid administration. In fact, pain involves a series of reactions also addressed to immunosuppression. The release of numerous substances from the site of the lesion contributes substantially to the immunological consequences of a surgical procedure (42). It is well known that surgery is associated with a diminished lymphoproliferative response proportional to the extent and invasiveness of the intervention, with alteration of the relationship between Th1 and Th2 cells and impairment of cellular immunity. The responses of the central nervous system and the hypothalamic–hypophyseal axis with respect to a major stress involves a complex network of signals that includes the release of catecholamines, endorphins, and cortisol. The release of these factors leads to a state of immunosuppression. On the other hand, the pain itself represents a stress that participates in the state of immunodepression, characterized by a reduction of NK lymphocytes (39).

Morphine administration for postoperative pain control is associated with a suppression of NK cells, compared to peridural analgesia, in a dose dependent manner (43). On the contrary, tramadol improved the activity of

NK both in operated and non-operated animals, and in subjects operated upon to remove a tumor (44). The interpretation is complex considering that the activity of NK is studied in vitro, in a neutral environment, rather than in real situations, subjected to a hormonal regulation of the organism in vivo. The use of experimental tumor models in animals has provided further information on the effect of opioids in the presence of a painful stimulus, reproducing an environment closer to reality. Indeed, NK cells control the development of metastases: while their absence favors metastasization, their production promotes resistance to metastases. In several studies the possibility of a benefit due to the administration of morphine for postoperative pain was studied in improving the resistance to metastases, reduced by neurohormonal factors affected by surgical stress. Other opioids such as tramadol and fentanyl seem to provide a better protection (38).

d) Chronic opioid administration and immune response

The need to study this phenomenon emerged from the finding that drug addicts showed signs of immunosuppression. In general, prolonged morphine administration makes the organism more susceptible to some types of infection or to cancer. In animals, the repeated administration of morphine reduced NK cells, promoted apoptosis of macrophages for an increase in NO-synthase expression, and caused a marked reduction in weight of the thymus and spleen, with a reduction in lymphoproliferative response attenuated by corticosteroid antagonists or adrenalectomy. These effects tended to disappear after a few weeks, suggesting the development of tolerance to the suppressive effects of morphine on NK. Also in this case, the administration of naloxone neutralized these effects. Morphine administration induced a shorter survival if it preceded the induction of experimental tumor, while the subsequent administration did not have a great influence. These differences therefore depend on the experimental conditions and timing. For example, while high doses may result in an important immunological stress, the implantation of a tumor at a distance of time may find the animal tolerant to the effects of morphine (38). A 12-week study investigated immune function in subjects with both malignant and non-malignant pain treated with slow-release morphine, but the results were inconclusive in terms of data interpretation (43). In some experimental models with melanoma cell injection and the production of hyperalgesia, morphine administration inhibited tumor growth and pulmonary metastases after tumor removal, thus providing more encouraging data in the treatment of cancer pain, considering the

important role of NK cells, normally inhibited by the administration of morphine, in the control of metastases (44).

-Immunosuppressive differences between opioids

Some experimental and clinical studies have highlighted a possible differentiation in the immunosuppressive activity among opioids. Buprenorphine in particular seems to be characterized by a minor influence on lymphocytic and macrophage function, even if the mechanisms have not been well elucidated. A lower propensity to activate the hypothalamic–hypophyseal axis or a minor activation of the vegetative system has been hypothesized, with a consequent reduced production of adrenaline and cortisol, and a lower impact on the lymphocyte function (38). In conclusion, the evidence seems to indicate that a single dose of morphine in the absence of pain may be immunosuppressive, but the clinical consequences from the biochemical data are unknown and depend on the circumstances in which exposure to the subsequent antigen occurs. On the other hand, the consequences of prolonged administration in the absence of pain seem to be associated with clinical consequences of an infectious order. The immunological effects of opioids in subjects with pain are more complex, especially for the experimental methodology and timing used not always being reproducible in the clinical setting. If pain is an important stressful event, opioid administration and adequate analgesia may compensate for any adverse effects.

Endocrine aspects

Although there is no evidence that endogenous corticosteroids influence the immunological sphere, exogenous corticosteroids are well known for their immunosuppressive activity. Opioid administration can activate the hypothalamic–hypophyseal axis with consequent alteration of lymphocytic proliferation (see below) (45). Reduced lymphocyte proliferation is associated with atrophy of the thymus and spleen, and adrenal hypertrophy, suggesting an increased corticosteroid response. This hypothesis is supported by the effects of adrenalectomy, resulting in a recovery of splenic and thymic activity. The corticotropin-releasing factor (CRH), like endogenous opioids, activates NK lymphocytes, while ACTH has minimal effects. Activation of the hypothalamic–hypophyseal axis with morphine produces a reduced activity of NK lymphocytes, a phenomenon not antagonized by adrenalectomy, suggesting a different mechanism. The primary and secondary lymphocytic organs are

innervated by the sympathetic system. Opioid administration induces an increase in the adrenergic response of the medulla, and the effects on NK cells appear mediated by this system, as demonstrated by block experiments with the use of sympatholytic agents (39).

Chronically administered opioids cause an upset of the hypothalamic–hypophyseal axis. Even if the effects are observable even early, the major consequences mainly concern the prolonged treatments applied to long-survivors and to patients with non-cancer pain. However, these effects seem to be reversible, with a recovery of hormonal activity at the suspension of treatment. Opioid endocrinopathy is present both during illicit use, in drug addicts for example, and for therapeutic treatments with opioids administered for various routes of administration, including the oral, transdermal, parenteral, and intrathecal ones. The most important and well-characterized syndrome is that related to androgen deficiency, with a reduction in the production of testosterone both in men and women. In women, in particular in subjects receiving methadone as maintenance treatment for addiction, a reduction in the secretion of luteinizing hormone is observed, associated with the appearance of a series of symptoms including amenorrhea or hypomenorrhea, weakness, depression, libido reduction, and osteoporosis. This dysfunction appears to be related to opioid doses, while the exclusive presence of pain would not be sufficient to induce such alterations. The appearance of these symptoms leads to an influence on the production of female sex hormones as well as on the reduction of androgens, with a cascade of hypothalamic-pituitary and adrenal events, and therefore with a consequent inhibition, both central and peripheral. Opioids reduce the activity of CRH, with a consequent reduction of ACTH and cortisol. The reduction of testosterone is consequent to these central perturbations, but also to a direct peripheral depressive effect at adrenal and ovarian levels, as demonstrated by the high plasma levels of testosterone present during systemic opioid therapy, compared to the relatively normal levels in patients undergoing intrathecal treatments, where ACTH levels are normal. These endocrine abnormalities may also have an influence on pain control with opioids. For example, it has been observed that correction with testosterone in such circumstances could reduce opioid consumption, reinforcing their clinical effect (46). Prolonged use of opioids intrathecally leads to dose-dependent hypogonadism in a high percentage of cases, with reduced plasma testosterone levels (47). Even patients with chronic non-cancer pain syndromes receiving continuous opioid treatment exhibit similar changes, such as those observed in patients on methadone maintenance therapy

(48). Many survivors who are still treated with opioids often report weakness, anxiety, and sexual dysfunction (49).

Hypogonadism involves the reduction of muscle mass, anemia, and cognitive abnormalities from chronic hypotestosteronemia (50). These problems recognize various causes including the debilitating effects of oncological treatments, the psychological problems related to the fear of recurrence and previous experiences, the depressive state, the use of multiple drugs. These hormonal alterations, however, do not seem to be attributable to the painful syndrome itself. The long-term effects of chronic opioid administration have only recently been studied and have revealed the prevalence of central hypogonadism with associated symptoms of sexual dysfunction, depression, anxiety, and fatigue, compared to the same cohort of patients who did not consume opioids (51). These effects appear to be reversible upon the discontinuation of opioid treatment (52). Furthermore, the hormonal response to the reduction of testosterone concentration that normally produces feedback on the hypothalamic–pituitary–gonadal axis, in particular of FSH and LH, is significantly reduced. The mechanism is unclear, but a possible explanation could be the pharmacological reproduction of an inhibitory physiological effect exerted by endogenous opioids in the regulation of the secretion of gonadotropins (46). This phenomenon could have as an intermediary modulator prolactin, whose secretion is increased by opioids, with a final inhibitory effect on the secretion of gonadotropins (53), although in some cases hypogonadism was observed in the presence of normal values of prolactinemia.

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CHAPTER NINETEEN C

OPIOID RESPONSIVENESS

Cancer pain can be effectively controlled in the majority of cases using opioids appropriately. However, treatments often lose efficacy because dose escalation is not followed by a favorable analgesic response and the therapeutic window is restricted by the development of side effects in attempts to increase the dose, despite the use of symptomatic drugs. The gradual increase in doses not being followed by a change in analgesic improvement should suggest that the treatment is inefficient or is bringing about a condition for increased neuronal excitability, a phenomenon known as opioid-induced hyperalgesia.

Opioid responsiveness can be defined as the degree of analgesia that can be obtained after optimization of the increase in the doses of an opioid, until adequate analgesia is achieved or, on the contrary, side effects develop. Various factors can interfere with a desirable favorable analgesic response, and are represented by disease progression, tolerance development, the tendency to develop side effects, pain mechanisms, the presence of some active or toxic metabolites, pharmacokinetic and pharmacodynamic factors, and genetic factors (1).

The response to opioids cannot be considered definitive after a treatment with a single opioid. The substitution of the opioid and/or route of administration has become a very effective approach to improving the performance of opioid treatment, overcoming the old concept of general responsivity to opioids. It is mainly based on a different characterization of opioid drugs which, though apparently similar, are able to determine different clinical responses in the same subject (1). This pharmacological technique allows the recovery of many clinical situations that were considered intractable and destined for recourse to invasive procedures which were often ineffective in the long-term, associated with severe complications, and not easy to manage over time.

Clinical aspects

Many factors have been identified that can condition the analgesic response, although the evaluation methods have not yet provided absolute answers. The Edmonton Classification System for Cancer Pain has been shown to predict pain management complexity based on various features, for example pain mechanism, incident pain, psychological distress, addictive behavior, and cognitive function (2). The integration of patient self-assessment tools with more objective clinician assessments can improve the classification of cancer pain. Patient-structured assessment of incident/breakthrough pain, neuropathic pain, and psychological distress significantly contributed to the discrimination of cancer patients with different pain levels (3). Incident pain, pain localization, opioid doses, use of nonsteroidal anti-inflammatory drugs, and sleep were associated with pain outcomes (4). However, identified domains explained 16% to 24% of the variability of the pain outcome. Initial pain intensity emerged as the strongest predictor of pain outcome after 2 weeks, and incident pain was confirmed to be a relevant domain.

- Neuropathic pain has always been considered a negative predictor, even if not absolutely. From a clinical point of view, neuropathic pain (see chapter 8) presents cellular biochemical modifications very similar to those described for opioid tolerance. In these situations there is a common cellular cascade, which involves the activation of NMDA receptors, resulting in a shift of the dose-response curve to morphine and a tendency to the development of hyperalgesia through a series of biomolecular events. This is an opposing force which stimulates an increase in the dose to achieve an equal analgesia. In other words, it is as if opioid tolerance was present in the absence of a previous exposure (1). It has been observed that neuropathic pain was more frequently associated with the use of strong opioids and adjuvants, and alterations at the cognitive, functional, and social level (5). Edmonton Classification System for Cancer Pain features were not predictive of pain management complexity at the follow-up visit when pain was managed by a palliative medicine specialist. However, patients with neuropathic pain were less likely to achieve their personalized pain goal (2).

- Breakthrough pain (see chapter 9), in particular its incident variant, with pain induced by activity in patients with bone metastases, is

certainly one of the most relevant clinical factors for the difficulty of finding a balance between background pain and pain on movement (6).

Patients may have no pain or mild pain at rest, but experience severe pain with physical activity, even minimal. An increase in opioid dose may improve mobility, but at the risk of adverse effects developing. A compromise between the occurrence of pain and activity has to be found.

- Pain intensity. Patients with moderate and severe pain have been reported to require a significantly longer time to achieve stable pain control and have required significantly higher final opioid doses (7). However, it is likely that non-homogeneous pain treatment biased the outcome. It is quite evident that in a temporal context pain intensity may be different in the different phases of treatment. It is more likely that prolonged periods of undertreatment may result in more distress and more difficulties in achieving pain control (8). In patients admitted to an acute palliative care unit, where more aggressive approaches of opioid dose titration were available, no correlation between baseline pain intensity categories and opioid response was found (9).

- Cognitive status. The early appearance of cognitive disorders is certainly one of the elements that condition the response to opioids. The presence of cognitive alterations has already been described as a possible factor leading to hyperexpression of pain intensity, so resulting in a more delicate condition, requiring expertise in the concomitant treatment of delirium and pain (see chapters 10 and 21b) (10). An inappropriate assessment may cause severe iatrogenic problems with undue opioid dose escalation (11).

Pharmacokinetic aspects

Some aspects of pharmacokinetics have already been examined in the chapter on opioid pharmacology (see chapter 16), in which it has been emphasized how the clinical expression in relation to the alterations of the metabolic pathways, dictated by the enzymatic polymorphism and possible interactions with other drugs, is variable. Some clinical conditions, related to age or to an alteration of the main organs of elimination, can also accentuate some effects. Some opioids produce active metabolites, especially under some conditions such as renal failure, and therefore the

clinical response will turn into toxicity, even if the relationship between the concentrations of these substances and the toxicity of the parent drug has not been well defined (see chapter 14).

Pharmacodynamic aspects

Other than the so-called pharmacokinetic tolerance, due to variations in the distribution or metabolism of drugs that influence the concentrations of the drug at the receptor site, such as in the case of an induced increase in metabolism, chronic opioid exposure can lead to two apparently different cellular processes, such as tolerance and greater sensitivity to pain (hyperalgesia). The convergence of these effects can reduce the efficacy of analgesia and complicate the clinical picture.

The development of tolerance is a phenomenon induced by the repeated administration of an opioid and determines a reduction of the therapeutic effect and the need to increase the dosage to maintain the same effect. There is an innate tolerance, linked to a genetically predetermined opioid sensitivity, which can already be observed after the first administration.

In the learning of tolerance a conditioning mechanism develops in particular environmental conditions associated with the administration of opioids, with the appearance of homeostatic mechanisms that tend to reduce the effect of the drug, that effect being restored if the opioid is administered under different circumstances instead.

Pharmacodynamic tolerance refers to a receptorial adaptation, in terms of density or desensitization, which confers a reduced response to a given opioid concentration (12). NMDA receptor activation seems probable, with cellular mechanisms very similar to those observed in neuropathic pain conditions (see chapter 8). Some opioids probably exhibit differences in their ability to induce tolerance. For example, a pharmacological property such as the intrinsic efficacy of opioids, that is, the ability to produce an effect with the involvement of fewer receptors, can be a prelude to a greater occupational reserve, inversely proportional to tolerance development capabilities, as in the case of methadone compared to morphine (1).

Opioids also show differences in the mechanism of the development of tolerance, in particular in the tendency to receptor internalization, a protective phenomenon that limits the intracellular counter-response leading to the production of ATP and of the opening to calcium channels (13, 14). For example, compared to morphine, methadone is a highly

internalizing drug, a factor that theoretically reduces the rate of development of tolerance.

The development of opioid tolerance is characterized by a shift to the right of the dose-response curve. It is dependent on the dose, time of administration, and receptor specificity, and is reversible. It also manifests itself acutely, for example, in the immediate postoperative period, and particularly with short-term drugs such as remifentanyl. In cancer pain, clinical experience has shown that many patients can maintain constant opioid doses for prolonged periods and that dose increases are often associated with disease progression. The maintenance of constant doses over time, and therefore a lack of tolerance development, seems to be determined by genetically induced counter-impulses (15). On the other hand, the establishment of tolerance for the side effects induced by opioids is quite rapid, with an important reduction in the frequency and the extent of symptoms such as nausea, present in 40% at the beginning of treatment, whose persistence would prevent a continuation of opioid therapy in most cases. Drowsiness and respiratory depression quickly go into tolerance. Constipation, on the other hand, is considered to be particularly resistant, although there are often other comorbid situations, such as dehydration, poor physical activity, weakness, and low nutritional intake, which may accentuate the persistence of this gastrointestinal discomfort.

Opioid-induced hyperalgesia

Many studies have shown that opioids can unexpectedly produce an increased response to pain stimuli (hyperalgesia) or pain induced by harmless stimuli (allodynia). This phenomenon is observed both acutely and chronically with high doses of opioids.

The repeated administration of opioids leads to a gradual reduction in the response threshold to nociceptive stimuli. This phenomenon is often observed in drug addicts or, for example, during an abstinence crisis. Patients undergoing methadone maintenance therapy have a lower nociceptive threshold. In patients with chronic pain, repeated administration of opioids under conditions of a lowering of the nociceptive threshold may lead to subliminal withdrawal conditions, to reductions in plasma concentration between boluses, and therefore to activation of cellular mechanisms that occur with an increase in progressive neuronal discharge and a further lowering of the nociceptive threshold (16).

The combination of these two phenomena appears clinically as a loss of analgesic efficacy, expressed as apparent tolerance, even if the contribution of the two entities is not evident or distinguishable. Therefore,

the reduction of analgesic efficacy should not be interpreted automatically as tolerance and consequently treated with an increase in dose, but should lead to accordingly careful consideration that an increase in pain symptoms may be due to tolerance, hyperalgesia, or disease progression.

Tolerance and sensitization

Sensitization refers to an increased response to a drug following repeated administration, a phenomenon known as inverse tolerance. From an adaptive point of view, tolerance and sensitization can be considered two strategies developed by the organism to adapt to environmental variations. Many experimental studies suggest that hyperalgesia and tolerance induced by opioid administration may share the same mechanisms present after a peripheral nerve damage. In all these conditions, a reduced morphine analgesia is observed. At the receptor level, chronic activation induces a compensatory increase in the formation of AMPc, which is a prelude to a state of cell excitation (17).

NMDA-type excitatory receptors have been shown to play a pilot role in the development and maintenance of hyper-excitatory states, such as hyperalgesia, allodynia, or spontaneous pain. The development of tolerance and hyperalgesia states is associated with the activation of glutamate receptors (NMDA). After a repeated high intensity stimulation activity, the activation of NMDA receptors initiates a cascade of intracellular molecular events, with an increase in the concentration of calcium and the activation of protein kinase (PKC). This removes the blockage of magnesium ions on the NMDA receptor and facilitates nitric oxide (NO) release, mediated by calciomodulin. The increase in the presence of PKC has been correlated with the appearance of hyperalgesia. The expression of NO-synthetase increases after important and lasting painful stimuli and the release of NO contributes to the appearance of hyperalgesia. Since NO is a diffusible gas, it is thought that it can be an important messenger in the signal transduction pathways that increases nociceptive information in the central nervous system. NO-synthetase inhibitors may reduce nerve injury-induced hyperalgesia by preventing or delaying the appearance of opioid tolerance. The same increase in intracellular Ca ++ stimulates further the activity of PCK, accentuating the subsequent feedback (1).

On the other hand, a series of studies suggests the presence of a biochemical relationship between NMDA receptors and opioid receptors. The activation of opioid receptors induces an activation of PKC, an enzyme that phosphorylates a series of proteins, such as the NMDA

receptor. The phosphorylation of this receptor induces the blockade of Mg ++ ions, facilitating Ca ++ entry, and a consequent activation of a cascade of events leading to a reduction of opioid receptor activity (down-regulation, tolerance), and a state of hyper-excitation with exaggerated response in the presence of painful stimuli (hyperalgesia). At the end of this cascade of events, there is an increase in the synthesis of nitric oxide (NO). These data are confirmed by studies performed with non-competitive NMDA receptor inhibitors or PKC synthesis inhibitors with regard to sensitization and tolerance development. These substances are able to prevent the sensitization, the development of tolerance, or the hyperalgesia precipitated by naloxone (17).

Glial and inflammatory cells have also been implicated in this complex mechanism that produces a progressive reduction of receptor activity and at the same time an increase in the excitatory response (18, 19).

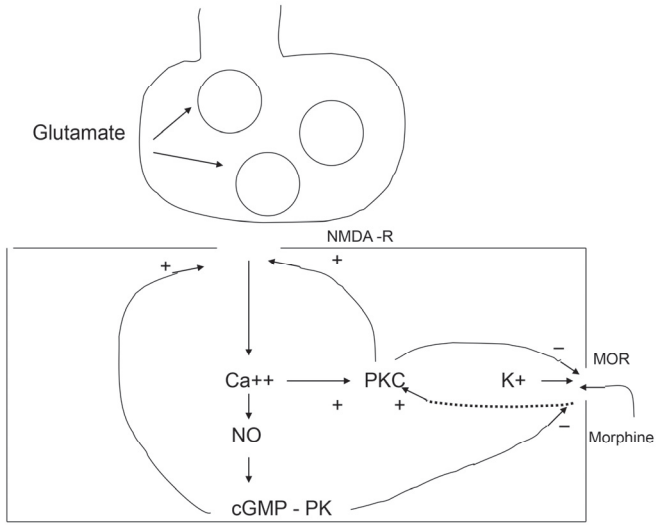


Fig.1. Activation of NMDA receptors increases the entry of Ca ++ to the intracellular level with a consequent increase in the activation of PKC and NO. The phosphorylation of substrates by PKC produces a further increase in the activity of the NMDA-Ca ++ receptor complex, with the development of a state of hyperactivity and decoupling of the G protein with mu receptor and consequent reduction of antinociception.

A common finding of a nerve injury or opioid-induced hyperalgesia is the increased expression of spinal dynorphin. The increased expression of dynorphin also seems to have implications in supporting the release of neurotransmitters, such as substance P. The effects of antidynorphin serum are very similar to those seen with NMDA-antagonist drugs, confirming that the dynorphin directly or indirectly interacts with the NMDA receptor. While the activation of NMDA receptors by glutamate induces a sensitization of spinal neurons, the blockade of these receptors, implemented with inhibitors, restores the analgesic activity of opioids, emphasizing the role of NMDA receptors in the development of tolerance and hyperalgesia. These processes are summarized schematically in figures 1, 2, and 3.

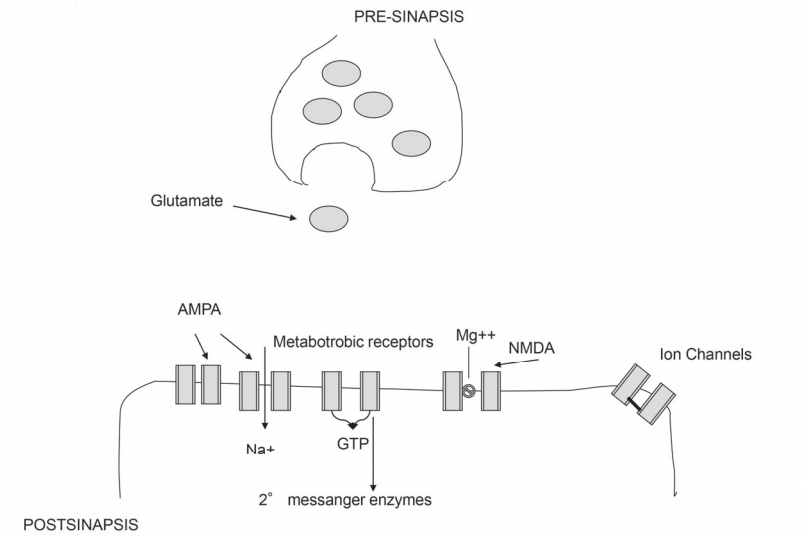


Fig.2. Normal synaptic transmission: Presynaptic activation produces glutamate socitosis that binds postsynaptic receptors:
Opening of the Na + and K + channels (AMPA receptors), and depolarization
The activation of metabotropic receptors facilitate the link between GTP and G protein and the activation of second messengers (PKC, adenyl cyclase).
The activation of NMDA receptors potentially induces the opening of the ion channels, inhibited by the flow of Mg ++

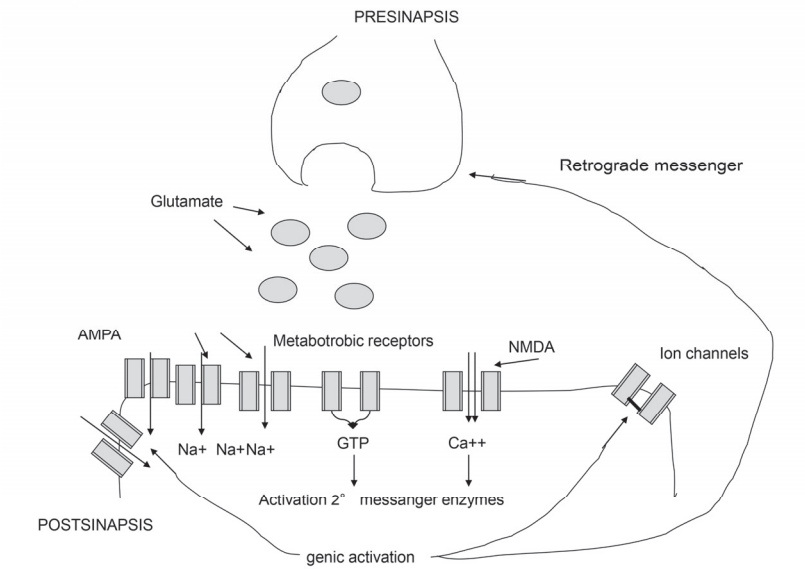


Fig.3. The intense and prolonged activation causes an abnormal release of glutamate. AMPA receptors are more activated, limiting the blockade offered by Mg ++ on NMDA receptors. Ca ++ crosses the channels interacting with the second messenger and producing a greater availability of AMPA receptors as a consequence of gene activation. The phosphorylation of ion channels makes the cell more excitable. Retrograde messengers are able to act also on the presynaptic zone favoring the release of further glutamate.

The descending system

The descending pathways of the nervous system play a fundamental role in the regulation of nociceptive transmission at the spinal level. The ventromedial medullary rectal area (RVM) includes the nucleus of the maphe magnum and the adjacent lateral reticular formation. A biphasic modulation with activation of the facilitation or inhibition of nociceptive processes was hypothesized for the activation of cell groups called “on-cells” and “off-cells”. The descending pathways are activated by tissue peripheral lesions to counterbalance the cascade of events that contribute to inflammatory hyperalgesia. The opiodergic circuits are consequently activated by increasing the inhibitory activity of the descending pathways, through the activation of the “off-cell” groups, and by decreasing the activity of the cellular facilitator groups, “on cells”. Even the serotonergic

and noradrenergic descending pathways suppress the responses of activated spinal neurons (see chapter 7).

The organization and the functional meaning of the facilitating network are less known and it produces contrary pro-nociceptive phenomena (20). The prolonged administration of opioids induces plastic modifications of the nervous system by activating cholecystokinin (CCK), a key mediator in increasing the excitation state of the descending inhibitory system, normally enabled to reduce the influence of the afferent information along the RVM. The reduced inhibitory activity of the descending system produces an uncontrolled activation of the expression of spinal dynorphin, already discussed previously, able in turn to promote the release of excitatory neurotransmitters, with a pro-nociceptive function that manifests itself clinically with an increase in the pain, attributed clinically to the appearance of tolerance (21) (figure 4).

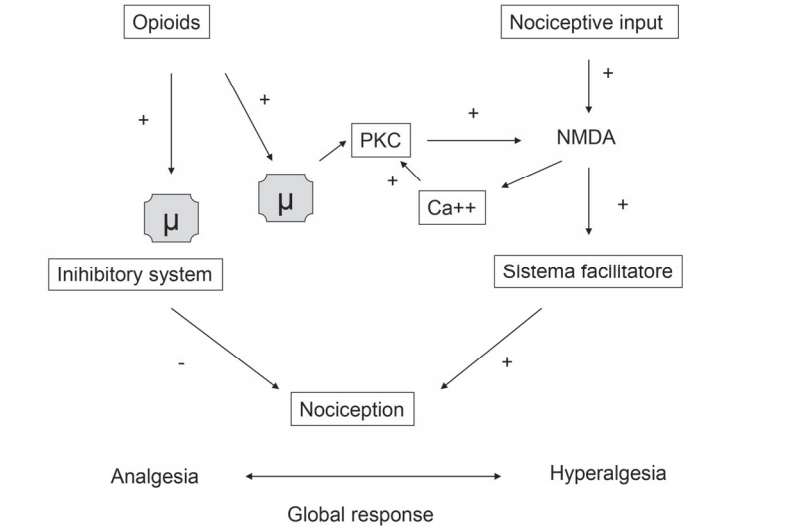


Fig 4. Components of the clinical response to opioids

Clinical implications

A reduced analgesia during opioid treatment is often evaluated as pharmacological tolerance if there are no evidence of disease progression, and an increase in dose is the natural solution. This conventional attitude hides pitfalls, because the anti-nociceptive effect is concomitantly

accompanied by the pro-nociceptive one, leading to a spinal excitatory turbulence. The overall clinical effect is affected by the balance of these two contrasting conditions. A missed analgesic effect or a worsening of the clinical situation should make us consider that tolerance is only apparent. There are also two other factors contributing to the loss of analgesia. The first is due to an increase in nociceptive activity, to a progression of the disease with an increase in mechanical, biochemical, and humoral stimuli, that is, an increase in the sensitization status along the nerve pathways, for further plastic mismatch to peripheral stimuli. The second is characterized by psychological implications, charged by anxiety and depression, by changes in cognitive status, and by behavior conditioned by pain, independently of the use of opioids (22) (see chapters 10 and 21b) (figure 5).

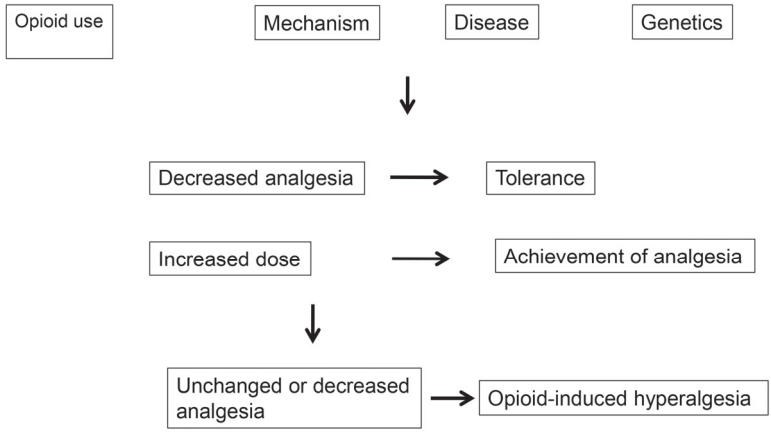
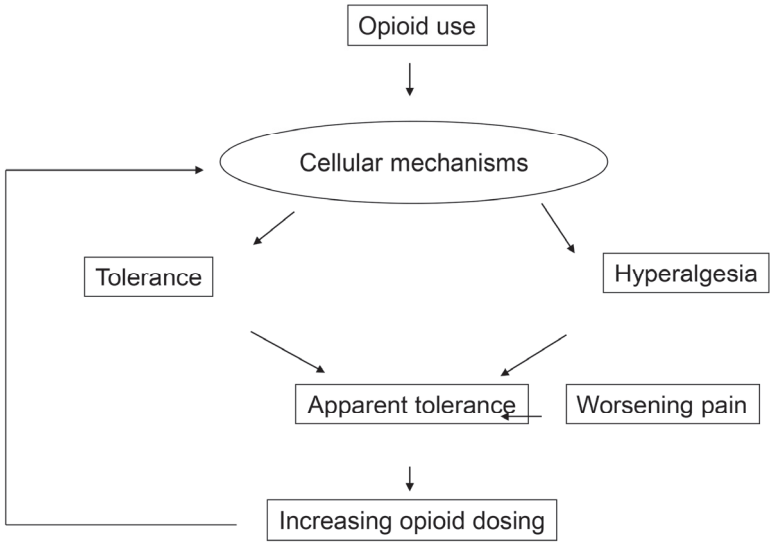


Fig 5. Evaluation of a state of poor analgesia evolving in hyperalgesia

It is therefore very difficult in the clinical setting to make a clear distinction between the two forms of pro-nociception, the pre-existing pain, and the lowering of the nociceptive threshold. In general, in the absence of evident progression of the disease, pain increases beyond the level of the previous level tend to generalize beyond the areas of distribution and appear less defined from the qualitative point of view because various nervous circuits and a multitude of molecular processes are involved. A qualitative assessment reveals changes in the pain threshold, tolerance to stimuli, and distribution. The administration regime could have an influence. Factors such as dose, duration, and type of opioid

may affect the development of hyperalgesia, even if these hypotheses remain only suppositions to be tested. Under-treatment of pre-existing pain or the development of tolerance can be overcome by an appropriate titration of the opioid dose. Unfortunately, even a prolonged underdosing can be a harbinger of a state of covered hyperalgesia, unmasked by the subsequent administration of opioids, as if such patients were in a state of potential abstinence with an accumulation of a state of medullary hyper-excitement. These patients will have a strongly altered response to opioids that are difficult to treat (8).



Further titration of opioids and a lack of analgesic effect after various dose increases should lead to a state of hyperalgesia. In this case the opioid dose should be reduced or better suspended and replaced with an alternative opioid (figure 6). The substitution of the opioid in such circumstances is quite complex, because the possible and approximate equianalgesia data are obviously not usable. The same discontinuation of the offending opioid could improve analgesia and minimal doses could be used to treat the true nociception (see chapter 19d). The use of anti-NMDA drugs could be a further option, to reduce the sensitization status (see chapter 13) (23). Alternatively, non-opioid analgesics such as anti-inflammatory drugs, or medications specifically adapted for a given mechanism of action, such as anticonvulsants and antidepressants in

neuropathic pain, may help reduce the dosage of the offending drug and allow the regaining of adequate analgesia. It has also been reported that some opioids possess anti-hyperalgesic properties besides analgesic effects, for example anti-NMDA activity, such as with methadone. This observation explains, as repeatedly reported, the unpredictability of the already difficult conversion ratios in patients who have undergone a rapid increase in the doses of the first opioid without success, probably developing hyperalgesia.

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CHAPTER NINETEEN D

OPIOID SUBSTITUTION (SWITCHING)

In cancer pain management there is no single opioid of choice for all patients (1). However, an opioid could be optimal for an individual patient in relation to a specific response to opioids determined by numerous factors (see chapter 19c) (2). As opioid response is not predictable a priori, previous opioid exposure can be considered a test to judge the responsiveness. Therefore, after the prescription of the first opioid dictated by criteria related to the clinical situation or more often by preferential individual choices, the clinical effectiveness is evaluated, in terms of balance between analgesia and side effects in relation to the dose used, and the stability of this condition over time. For example, effectiveness may gradually fade and dose increases be required. In some cases progressive dose increases do not produce the desired effects or produce unmanageable side effects (2). In these circumstances, the initial opioid should be discontinued in favor of a second opioid. This process is commonly called opioid switching or opioid rotation and aims to improve the clinical response (3).

Rationale concerning the differences between the various opioids

As reported in the previous chapter, a clear difference in the individual receptor profile has been highlighted. The receptor constitution depends on genetic polymorphisms, which include variants that alter the sequence of amino acids, as well as the properties of the receptor function. Some variants may exhibit alterations of binding affinities. Receptor subtypes may be dimers that offer different signals than monomers (4). While it can be presumed that tolerability to an opioid manifests itself early, changes over time may be due to changes in density and receptor properties after prolonged exposure or as a consequence of disease progression, due to the relationship between receptors and humoral factors. Therefore, the response to opioids can change over time even after an initial phase of

responsiveness. Thus, a receptor mutation contributes to the change in inter-intra-individual variability of clinical opioid effects (5) (see chapter 15).

The μ-agonists have traditionally been considered similar to morphine. In recent years this assertion has been strongly questioned. Repeated administration of opioids determines the development of tolerance, which can shift the dose-response curve (see chapter 19c). The development of tolerance to the different clinical effects of opioids can be dissociated over time and the amplitude of cross tolerance between opioids can vary greatly (2). When the tolerance to adverse effects does not develop at the same rate of analgesia, further dose increases induce the prevalence of side effects. Therefore, the different clinical response in different subjects is the result of an asymmetric cross-tolerance between different opioids. Tolerance develops independently in each sub-receptor group or in different variants in response to an opioid binding and its intrinsic capacity. Receptor activation induces a reduced sensitivity to the μ-agonist and an adaptation of the neuronal system through the expression of compensatory mechanisms (6). Variations in the opioid-receptor ratio may vary over time during the disease progression with prolonged opioid administration, resulting in a change in the balance between analgesia and side effects. The phenomenon of asymmetric cross-tolerance may also be due to differences in efficacy rather than selectivity (7) (see chapter 19c).

Pharmacokinetic differences between opioids have already been described in previous chapters. These changes in absorption, metabolism, and elimination, and the related polymorphisms and interaction potentials, may explain the changes in the clinical response when substituting one opioid with another.

Frequency, indications, effectiveness

Initial studies on opioid switching have reported clinical improvement in about 3/4 of patients using lower doses compared to equianalgesic tables (8-10). Several subsequent studies have provided increasingly clear information. A frequency of 21-44% of patients receiving opioids has been reported, with more frequent use in certain more specialized environments (11-13). Even in outpatients, even in specialized centers, the frequency is high, although using lower doses (14).

The efficacy of substitution seems quite high, ranging 50-90% of patients in more recent studies (15). Generally, switching is considered effective when at least a 33% reduction in pain intensity or side effects is achieved compared to previous values (16).

Initially the indication to switch was represented by the appearance of side effects before reaching analgesia. The absence of side effects could in fact induce a further increase in doses in the attempt to reach analgesia according to the belief of the lack of ceiling effect of strong opioids (17). As described in the previous section, there are many conditions in which switching could be anticipated, for example in patients in whom dose increases are unsuccessful, suggesting the suspicion of progressive tolerance and/or hyperalgesia. While there is obviously no specific dose, it will be the clinical context that will suggest the right time to stop the escalation of doses, even before side effects appear. For example, a patient who has doubled or tripled the dose in a few days without having a minimum benefit, in the absence of clinical situations that could explain the worsening, is likely to be a candidate for switching. Therefore, the escalation index, which calculates the increase in dose over time, could be a very useful parameter (18). The phenomenon of opioid-induced hyperalgesia poses serious conversion problems, especially when methadone, which has other extra-opioid effects, is chosen for opioid switching. The isomer D can attenuate the development of tolerance and hyperalgesia (19, 20). In neuronal hyper-excitation states, the anti-NMDA and noradrenergic effects of methadone can produce unpredictable effects, beyond the expected effect on the opioid receptor (21). Therefore, the use of methadone in these circumstances is particularly complex and should be individualized, possibly in a specialized environment where the clinical response can be more closely monitored.

In addition to uncontrolled pain, or conditions in which side effects prevail or when uncontrolled pain persists despite increasing doses of opioids with high escalation, some patients may be switched for convenience, for example due to poor compliance or unavailability of the previous route of administration. This occurs, for example, with the use of the parenteral route to replace the oral route when it is no longer available (22).

Conversion ratios

The concept of equianalgesia refers to the theory that different doses of opioids can produce a similar level of analgesia based on their potency. Conversion tables are not always feasible for contexts in which it is difficult to reproduce a similarity in the clinical setting, particularly in complex situations where a balance between analgesia and side effects is sought, rather than obtaining the same level of analgesia, as can occur under stable conditions (for example when switching is used for convenience). In general

it is suggested to decrease the dose by 1/3 or half compared to the conversion tables (23). The choice of conversion ratios to be used should not be entrusted to a mere mathematical calculation, but should consider an evaluation of previous treatments, the intensity of pain and the tendency to develop side effects, comorbidity, concomitant use of others drugs, and the exclusion of pharmacokinetic factors that may compromise the efficacy of certain opioids. Approximate equianalgesic dosages that could be used as conversion ratios for switching are described in table 1.

Oral morphine	60 (20)
Tapentadol	200
Oral oxycodone	40
Oral hydromorphone	12
Oral methadone	12 (8-10)
Transdermal Fentanyl	0.6 (0.5)
Transdermal Buprenorphine	0.8 (0.6)

Table 1. Approximate ratios of equipotence among the principal opioids expressed in mg (in brackets via parenteral), to be used for convenience

Some recommendations for conversion ratios between opioids during switching have been produced (24).

- Hydromorphone. Opioids with similar pharmacokinetic characteristics appear to maintain relatively stable conversion ratios with hydromorphone. Most studies suggest an approximate hydromorphone-morphine ratio of 1:5, with oxycodone 1:4, with transdermal fentanyl 15:1.

- Oxycodone. There is some relevant evidence for a recommendation of an approximate morphine-oxycodone conversion ratio of 1.5:1.

- Transdermal opioids. Switching to transdermal opioids is generally recommended in patients in stable conditions (for convenience), unless treatment is assisted in the early days with other drugs until stabilization is achieved. There is some evidence that 0.8 mg of transdermal buprenorphine (35 μg/h) and 0.6 mg (25 μg/h) of transdermal fentanyl are equivalent to 60 mg of oral morphine equivalents. The ratio of 1:100 between transdermal fentanyl and oral morphine seems to be fairly reliable in both directions. There

is a certain consistency to consider a ratio between 1:15 and 1:20 between transdermal fentanyl and methadone. Unlike what is reported with morphine and hydromorphone, this ratio does not seem to be affected by the dose of the first drug.

- Methadone. While for the other morphine-mimetic drugs the conversion ratio seems to be predictable, the substitution with methadone has always been considered more problematic. A certain relationship has been reported between the previous dose of opioids, such as morphine and hydromorphone, and the conversion ratio with methadone: the higher the dose of the opioid to be substituted, the greater was the conversion ratio, i.e., the lower was the dosage of methadone (25), even though on average the final stabilization ratio reached was 1/6, with wide individual variations (26). The final conversion ratio has been somewhat variable and individual (2:1-15:1) (27).

In particular, methadone switching after a prolonged phase of opioid escalation poses significant problems, as any reference is missing. Probably in these patients, the conversion ratio could be higher, as if a high index of escalation would be a sign of neurotoxicity, that is, an adverse effect, thus suggesting that the offending drug is to be discontinued (20). In fact, the same suspension of the drug imputed of inducing hyperalgesia should allow a consequent clinical advantage. Therefore, there are clinical conditions that suggest changing the conversion ratio with methadone with some flexibility (table 2).

Side effects	↓ dose (↑ ratio)
Uncontrolled pain	↑ dose (↓ ratio)
Both	↓ dose (↑ ratio)
High escalation index	↓↓ dose (↑ ratio)
Convenience	= ↓ dose

Table 2. Factors that influence conversion ratios with methadone

Methadone, with its peculiar pharmacological peculiarities, can interrupt the vicious circle of tolerance and hyperalgesia. A very conservative conversion ratio has been suggested for patients receiving high doses of the first opioid using maximal methadone doses of 30 mg/day (28). Alternatively, it may be reasonable to go back to the dosage of the first

opioid at the beginning of the escalation and calculate the ratio existing at that time (20, 21).

Modality of switching

Choosing a switching model is not easy, especially when methadone is used. As already pointed out, methadone has extra-opioid effects, does not have a linear kinetics, and is prone to multiple possibilities of drug interaction. These properties make it difficult to predict a conversion ratio. Early studies have suggested using doses inversely proportional to the dose of the first opioid, also suggesting a gradual introduction and the suspension of methadone and the first opioid, respectively (adding 1/3 of the calculated dose per day for three days, and reducing 1/3 of the previous drug dose for three days (3D) (25). This approach requires many days for clinical stabilization, ranging 3-11 days, with unavoidable consequences for a patient deemed highly suffering.

Another strategy suggests giving methadone when needed, with a conversion ratio of 1:10, with a maximum of 100 mg/day and with block intervals of at least 3 hours (29), with some variations, for example every 3 hours but no more than 40 mg (30). When the requests become stable, the daily dose is divided into two administrations. The stop & go strategy (SAG) assumes that an unfavorable clinical condition requires immediate discontinuation of the offending drug and an immediate substitution with methadone using a strong ratio (5:1) to overcome the slow induction resulting from the large volume of distribution of the drug, and to achieve effective concentrations in a limited time. This ratio is also useful for testing the response that subsequently allows the dosage to be modulated in relation to the clinical situation, rather than using numerical rules, and above all to obtain a clinical result in the short term (less than three days on average) (31). This approach has pharmacokinetic advantages, producing an induction priming with rapid inverse changes in the plasma concentration of the two opioids and especially removing the persistent metabolites, as in the case of morphine. This technique requires some clinical flexibility, and above all a particularly specialized environment where patients are frequently evaluated.

Switching with transdermal drugs presents considerable difficulties, due to the slowness in obtaining stable concentrations in otherwise unstable patients. Viceversa, substitution for convenience, that is in conditions of stability, can be implemented more simply and with fairly predictable results (32).

Existing studies regarding changes in opioid concentration during switching provide an idea, albeit approximate, as to what happens in these circumstances, even if plasma concentrations do not accurately reflect clinical events. Morphine, and in a slower way its metabolites, are removed in 24-72 hours, while active methadone concentrations are obtained in 24-48 hours, above all by priming, as in the case of SAG, suggesting that this method allows a faster removal of the offending drug present in high concentrations before switching (33). Even with the transdermal-methadone fentanyl sequence with SAG, the concentrations of fentanyl decay slowly, while those of methadone progressively increase, as if the space filled by the first drug is substituted with a superimposable timing with methadone (34), limiting the risk of overlapping effects of the two drugs. A delay of administration of methadone with respect to the removal of the patch is therefore not justified (32), especially in the case of a patient with high pain intensity, because it would risk leaving the patient with a completely uncovered analgesic window.

Factors that influence the use of switching

In various studies, many factors such as age, type of pain, and the use of adjuvant drugs, have not shown a major influence on the need for switching, apart from the use of corticosteroids (which would presumably be protective). The use of hydrophilic opioids and their metabolites in the presence of renal failure was more frequently associated with switching (10, 13). In other studies, the number of white blood cells and platelets, weight, the use of antiemetics, gastroprotectors, a recent chemotherapeutic treatment, low intestinal tumors, and the use of beta blockers were considered predictive factors (35), but also these findings have not then been confirmed. More advanced patients receiving prolonged opioid treatment are more likely to get switchers (36).

Another type of analysis that has been performed concerns the factors that influence the conversion ratio. Indications to switch seem to play a role (27). Switching for side effects is associated with a high ratio and therefore at a lower dose of methadone, while if the cause is uncontrolled pain, exactly the reverse occurs (14). Age, sex, and type of pain, for example neuropathic pain, do not seem to significantly influence the final conversion ratio (23, 37).

Switching in the opposite direction

The direction of switching may be problematic, as the ratio may not be identical when reversing the sequence. The substitution of methadone, a broad-spectrum opioid, to another drug not having such characteristics could be unfavorable and produce an increased intensity of pain (38, 39). Indeed, the use of methadone is not an irreversible condition from which one cannot go back. In clinical practice it is possible to regain a good clinical balance by substituting methadone with other opioids (25, 40).

Mortality

It has been reported that switching can be fatal due to the risk of overdose (41). Actually, single-case reports were determined by outdated conversion ratios, poor monitoring, or prescription errors. Less survival can be observed in patients with poor performance status and opioid-induced neurotoxicity, or with switching failure, elements that are more frequent in the end stages of life (42), where clinical responses are much more complex, possibly due to the presence of stressful symptoms that influence pain assessment (20, 36).

Evidence

No controlled study has investigated the efficacy of switching (43). The recommendations are derived from retrospective or observational studies (23), which are not able to provide strong evidence. This poor evidence is even reported for the use of opioids which are strongly recommended as a milestone in cancer pain therapy (44). Therefore, the lack of evidence should not discourage the use of an ever more widespread pharmacological technique which has greatly reduced the need for interventional procedures.

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CHAPTER TWENTY

INVASIVE PROCEDURES

In very select cases it may be useful to undertake alternative treatments that may limit the escalation of opioid doses, especially if conditions of poor responsiveness with an unfavorable balance between analgesia and side effects develop. Some sites can be more easily and less riskily attacked and their blockage can offer better guarantees of quality of life for the patient.

Good quality studies existing in this field are quite limited, with the sole exception of the celiac plexus block. Therefore, the rather optimistic view of the interventionists does not go beyond a small number of cases generally of little scientific importance, often contradicted by numerous reports on immediate and late complications, especially concerning somatic blocks, whose complex innervation is often not exactly as expected. Cancer pain is complex, as it involves multiple mechanisms and often in distant sites or in any case not strictly covered by nerve innervation. Furthermore, the use of these techniques is often not followed by an appropriate continuous care, as performed in other settings.

Analgesic blocks must always be preceded by a careful evaluation of the pain syndrome and the probability of evolution in relation to the previous treatment, and by a detailed explanation of the advantages and success rates in relation to the analgesic treatment to be carried out and the desirable results to be obtained. Simpler and less risky procedures should be preferred (1).

Peripheral somatic blocks

In the peripheral nervous system there is a considerable individual anatomical variability. Sensory innervation is even more complex due to the overlapping of areas served by different nerves, such as in the thoracic region. Furthermore, analgesia can correspond to an anesthesia or a motor block not always pleasant for patients. Neurolytic blocks are also not definitive, are burdened by important complications, and can induce

serious deafferentation syndromes, although unlikely in cancer patients due to the limited life expectancy.

In a recent review, no controlled study was evidenced and therefore the effectiveness of these blocks is to be considered exclusively anecdotal, beyond the good short-term results reported (2). The most common peripheral blocks include the brachial plexus block, suprascapular nerve block, intrapleural block, intercostal block, lumbar plexus block, and penile blockage.

Intrathecal neurolysis is practiced less and less often thanks to the greater experiences achieved with modulation techniques that have strongly overcome this technique in relation to the high number of major complications. These include dysesthetic pain, muscle paresis, anesthesia and hypoesthesia, and sphincter disorders. However, in some very select cases the blockage can be useful in the overall economy of an analgesic treatment. In particular, patients with existing sphincter disorders, colostomized or with a bladder catheter, have an obvious reduction in the risk of permanent injury. Alcohol or phenol are used. Considering the different baricity, these substances require opposite positions on the operating table during the injection and for a certain period, to wet the posterior part of the spinal roots and to save the anterior medullar structures, in an attempt to preserve the motor activity.

The theoretical advantage of the epidural injection of phenol consists in a lower incidence and severity of side effects, even with the use of repeated low doses through a catheter. The onset of effect is longer and the distribution of analgesia less predictable.

In contrast to non-cancer neurological syndromes, such as trigeminal neuralgia, cancer pain due to head and neck cancer is produced with the variously combined and complex involvement of cranial nerves and intracranial nerve ganglia. Therefore, it is rarely that neurolysic techniques, even performed correctly, will result in a complete resolution of pain. The most frequent occurrence in head and neck tumors in which it is possible to evaluate a possible neural block is the invasion, by contiguity, of the cranial base and the nervous structures emerging from it by tumors of the rhinopharynx, of the jaw, and ponto-cerebellar angle.

Pains due to infiltration of the tonsil palatina, of the retropharynx, and of the posterior part of the tongue can involve the glossopharyngeal nerve determining pain syndromes of particular intensity. Spontaneous pain is violent and radiates to the neck and the ear canal up to the tragus. It is accentuated in attacks and paroxysms by swallowing and phonation. Furthermore, the patient’s situation is made more painful by an intense associated sialorrhea. The thermal lesion (always obtained with

radiofrequency) of the glossopharyngeal involves the positioning of a needle under fluoroscopic control in the most medial angle of the jugular foramen where the petrosal ganglion is located in connection with the emergence of the glossopharyngeal (3).

Sympathetic blocks

The sympathetic nervous system is involved in various forms of cancer pain in which there is a lesion of the nervous system (Pancoast syndrome, sympathetic-reflex dystrophy in the limbs). In many cases, however, the transport of the painful sensation occurs exclusively by the sympathetic system (abdominal organs). The interruption of these pathways therefore allows us to abolish the painful sensation without producing sensory or motor alterations, unavoidable with somatic blocks, and without the risk therefore of iatrogenic syndromes from deafferentation.

a) Celiac plexus block

The block of the celiac plexus is probably the block with the highest efficacy-complication index and the most studied one. It consists in the injection of a neurolytic substance (alcohol or phenol) into a large ganglionic group located in the epigastric site posterior to the stomach and pancreas, and anterior to the crura of the diaphragm. The main indication is represented by pain of visceral origin coming from the upper abdominal area, as in the case of primary tumors of the pancreas, stomach, liver, and gallbladder. The involvement of somatic structures such as the peritoneum and the abdominal wall therefore excludes the possibility of effective pain control.

A good success has been invariably reported, in more than 85% of patients undergoing this procedure. In a recent literature review the quality of the studies was generally low due to a number of methodological limitations. However, at least two controlled studies of good quality and large numbers have confirmed the efficacy of celiac plexus blockade in producing analgesia and/or reducing opioid consumption (4).

Many patients agree to undergo this procedure, because of the relatively low risk of complications, which allows the use of reduced opioid doses, with a slower escalation over a prolonged period of time. As a consequence the gastrointestinal symptoms (nausea and constipation) related to opioid administration or the disease are of reduced intensity. If necessary and if the clinical conditions allow it, the block will be repeated. The main problem to have emerged in recent years concerns the timing of

execution. It is believed that an extreme use in the advanced stages of the disease is less helpful due to the high probability that the disease has exceeded the visceral elements, to involve somatic structures, for example the peritoneum or the muscular structures, not affected by the block (5). On the other hand, an early execution in the absence of a high intensity of pain or a certain opioid consumption is unlikely in terms of possible future benefits, since it is not possible to predict the severity of pain in the individual (6).

Serious neurological complications are very rare. Paraplegia is the most fearful, albeit rare, complication of the neurolytic block of the celiac plexus. Spinal cord damage is attributed to the chemical or mechanical lesion of the anterior root artery, perhaps due to the use of high concentrations or injected volumes, although recent experimental data do not confirm an important spastic activity of alcohol or phenol.

Hypotension, linked to the loss of sympathetic tone with consequent splanchnic vasodilation, is more frequent in the elderly and generally tends to self-limit after the first few days. A generous use of plasma-expanders during the procedure and within 24 hours, associated with lifting or compression with elastic bands of the lower limbs, is able to prevent this problem.

The procedure is the most studied in the literature. Some good studies have shown that the blockage of the celiac plexus reduces the intensity of pain and the consumption of opioids (7).

- Superior hypogastric plexus block

This has been used in pelvic pain from primitive gynecological tumors. Positive results have been reported in 70% of cases, even if there is no objective finding of the magnitude and duration of the analgesic effect. Pelvic pain due to neoplastic growth or anticancer treatments is rarely exclusively visceral in nature, unlike abdominal sites. The presence of bone involvement and neurological involvement limits the effectiveness of a sympathetic block. Possible complications are urinary or rectal incontinence, perforation of viscera, or intravascular injection (8). The data are less conclusive than the block of the celiac plexus because there are no well-conducted studies of sufficient quality and number of patients. Finally proposed was the block of Walther's ganglion for perineal pain of sympathetic origin (rectal infiltration and vagina). Also, in this case the somatic component can influence the pain syndrome and limit the advantage of the technique (7). However, this technique can be individually chosen on the basis of specific clinical conditions.

A 48-year-old woman with a history of ovarian cancer was admitted to the Main regional center for pain relief and supportive care. She had undergone surgery and different courses of chemotherapy, a course of pelvic radiotherapy, and a further intervention for removing a relapse to pelvic lymph-nodes, also requiring an implantation of a ureteral stent. She presented with persistent abdominal pain in the right inferior quadrant, and perineal pain. She had been treated with different lines of opioids and before admission she was receiving transdermal fentanyl 3.6 mg/day (150 mcg/h), ibuprofen 800 mg/day, and subcutaneous morphine 10 mg as needed, administered 4-6 times a day for super imposed episodes of breakthrough pain. Pain intensity was 7/10 with peaks of breakthrough pain of 10/10, occurring 4-6 times/day. Fentanyl was switched for methadone in doses of 90 mg/day orally, without reporting any clinical benefit. A ketamine burst of 100 mg/day and midazolam 30 mg/day for two days was uneventful. A further increase in methadone doses did not improve the clinical condition. A superior hypogastric plexus and Walther's ganglium neurolysis were proposed to the patient as an alternative to improve this miserable condition. The day after the procedure, pain intensity was 0/10. Methadone doses were progressively reduced to 45 mg/day orally. The patient was discharged in an absolute pain control.

The patient complained of a lower abdominal pain associated with perineal pain. These areas are the main target for the two blocks used in this patient: the superior hypogastric plexus carries afferents from the viscera of the lower abdomen and pelvis, and the ganglion impair innervates the perineum, also including distal rectum, anus, distal urethra, vulva, and distal third of the vagina. The neurolysis of these sympathetic nerves provided an excellent analgesia, also allowing a reduction of opioid doses.

The spinal route

Spinal analgesia can be an effective method to control pain in difficult situations, where the response to systemic opioids is insufficient or associated with uncontrollable side effects. The rationale is based on the administration of reduced doses of opioids near the spinal cord, where the opioid receptors are widely represented, reaching effective concentrations and potentially reducing the side effects produced by high doses of systemic opioids.

One of the main problems is the selection of patients to be treated with spinal analgesia, to prevent the temptation of over-utilization of the

technique by untrained personnel in the use of opioids. In fact, patients should have been subjected to an optimization of the use of opioids, i.e., an individualized treatment with various opioids and routes of administration, and an appropriate use of adjuvant drugs to improve analgesia or limit side effects beforehand in order to consider the clinical condition refractory to pharmacological treatment. With an appropriate selection, the recourse to the technique is really limited to less than 1% of patients (9). The spinal route should therefore be reserved only for selected cases, treated with at least three opioids and/or two routes of administration with unsatisfactory results before proposing a spinal treatment. The decision will however be considered as there will be the logistical prerequisites for a good continuation of extra-hospital treatment.

A very controversial study on the use of an implantable system for the administration of intrathecal morphine has reported an important result compared to traditional pharmacological treatment, with better analgesia, fewer side effects, and a greater survival (10). However, the study presented many methodological flaws and above all an inapplicability in the real world. An unclear trial (epidural, injection or infusion), the lack of differences in pain control, the lack of clarity on the use of local anesthetics and their doses, patient selection, concomitant treatments, an imprecise protocol for the administration of opioids in the traditional arm, the extent of complications related to the technique, and some statistical considerations make the meaning unreliable (9).

By spinal route, morphine seems to offer indisputable advantages over other drugs: it has a higher power ratio than the systemic route, compared to what happens with other lipophilic agents such as fentanyl. Intrathecal morphine tends to provide a central effect due to the tendency to spread cranially, which also produces a prolonged effect. The conversion ratio with the oral route, at least in tolerant patients already receiving ineffective treatments with systemic opioids, should be about 100:1. The greatest benefit of the spinal route is to be attributed to local anesthetics, which provide a formidable adjuvant action to analgesia with opioids, because their addition produces an analgesia by a completely different mechanism (9). Their dose is conditioned by the effects on motor activity, which should not be altered for a good clinical result. Generally, doses of 25 mg/day of bupivacaine are well tolerated and do not lead to significant side effects.

From a practical point of view, a certain amount of morphine, in doses substantially reduced (about 30%), is continued to avoid peripheral withdrawal symptoms and the conversion from the oral to the intrathecal route is used (see table 1), adding to the infusion a mixture 25 mg/day of

bupivacaine, and providing a certain volume to promote the spread in the chosen metameric site (about 2 ml/h). The dose of systemic morphine will subsequently be modified according to the clinical response. Subsequently, the doses of intrathecal morphine can be modified, while a dose of 50 mg/day of bupivacaine should not be exceeded. Because of the need to administer discrete volumes, it is necessary to use external pumps, rather than implantable systems, burdened by numerous technical complications. The use of a subcutaneous port connected to an external pump is more convenient for manageability, less technical problems, and above all the possibility of modifying the dosage in an easier way. The use of the epidural route, on the other hand, should be proscribed for the quantity of technical problems and above all for the difficult management in terms of dosages and volumes.

- Reduction of systemic opioid doses at 30% - Intrathecal infusion Morphine (1/100 of the oral dose): example 300 mg oral = 3 mg intrathecal Bupivacaine 25 mg Saline to achieve a volume able to provide 2 ml/h (48 ml/day)

Table 1. Use of intrathecal morphine-bupivacaine combination

Minimally invasive vertebral procedures

Vertebral metastases are quite common in cancer patients. In the presence of vertebral metastases, a loss of structural integrity is observed, which is accompanied by stimulation of the painful fibers with minimal pressure loading, due to physical activity. The treatment of vertebral bone pain can be quite complex. Therapeutic options include a combination of treatments, such as chemotherapy, radiotherapy, orthopedic decompression and stabilization surgery, and a symptomatic treatment with analgesics. Movement pain associated with spinal metastases can be difficult to control due to sudden and unpredictable onset even for minimal physical activity (see chapter 9). The use of increasing doses of the selected opioids not addressed to the background pain control but to a better mobilization often results in important side effects at rest.

Vertebroplasty and kyphoplasty are performed with the injection of bone cement (polymethylmethacrylate) into the fractured area of the vertebral body through a uni-bipeduncular approach, with the aim of restoring the integrity of the bone and preventing its collapse (11). Cement

allows a structuring of the vertebral body, potentially reducing pain, since the cement also has an intrinsic and antitumor analgesic effect. In kyphoplasty, cement is injected after creating a balloon swollen cavity that allows a low pressure injection, thereby minimizing the extra-injection complications (12). Complications are rare, but they can be serious. Cement can escape from the vertebral body posteriorly into the spinal canal, through the vertebral foramina or anteriorly towards the paraspinous veins (13, 14). Pulmonary embolism is potentially possible (15). While the incidence of these complications is quite low, patients with bone metastases are at greater risk than osteoporotic individuals. Pain may persist after the procedure, even for the redistribution of the column weights, as well as for radiculopathy. Finally, radiofrequency ablation is proposed to abolish the tumor in the vertebral site. Cryoplasty, produced by the expansion of argon in the lesion with the formation of an ice ball, produces dehydration and cell death.

Few studies have evaluated these techniques in the cancer patient. Among these techniques there is only a controlled study in favor of kyphoplasty, while for the other techniques the recommendation is very weak due to the poor quality of the available studies (16).

Percutaneous cordotomy

Percutaneous cordotomy is a technique used to interrupt the spinothalamic tract in the anterolateral quadrant, the most important ascending pathway for transporting nociceptive information through a lesion produced by radiofrequencies. It is carried out at the cervical level between C1 and C2 where the fibers are more compact and have a more precise position, the lumbosacral fibers are in lateral position, while the cervico-thoracic fibers are more ventral giving more selective indications according to clinical circumstances. Correct cordotomy causes profound analgesia in the contralateral side of the lesion, which can extend into the C3 to S5 dermatomes, also producing a Claude-Bernard Horner syndrome with sympathetic hemiblock homolateral to the lesion (17). However, as cordotomy is an intervention that is difficult to perform, in order to obtain these percentages of success, prolonged training of the operator is mandatory. Although success is reported in a high percentage of cases (74-94%), adequate and lasting monitoring is often not reported. The technique also has a certain mortality and morbidity. In some patients, after cordotomy pain may remain. A contralateral pain to the cordotomy lesion (treated side) is a very serious and bothersome complication, linked to a deafferentation that appears in 10-15% of patients. Other complications

include transient effects such as fever, headache/cervicalgia, orthostatic hypotension, urinary retention, hyposthenia/asthenia and permanent complications of motor disorders (incidence of paresis ranging from 0-15% in different cases), bladder function disorders (urinary retention in 2-18% of cases), and disorders of respiratory function. Cordotomy, in fact, can cause alterations in the respiratory function of different entities depending on the extent of the lesion determined at the level of the spinal cord. In the case of unilateral cordotomy, these alterations, consisting mainly of small variations in vital capacity, maximum respiratory capacity, and respiratory muscle strength, are clinically silent and can only be detected through functional tests. Perioperative mortality ranges from 0 to 5% and is statistically correlated with the presence of a severe preoperative respiratory deficit and reduced patient status, additionally to the experience of the operator (1). Beyond the enthusiasm of the operators for an apparently magic intervention, there is no unanimous opinion about the indications of cordotomy in the patient with cancer pain (18). Some pain syndromes, such as Pancoast's syndrome, costopleural pain, lumbosacral plexopathy, and some resistant forms of incident pain, could be an indication for the use of this technique, burdened by the obvious limitations of a high percentage of serious complications.

Pituitary neuroadenolysis (NALP)

This consists in the injection of alcohol (1-2 ml) into the pars distalis of the pituitary, through a needle introduced under fluoroscopy via rhino-transfenoidal hole in the posterior apex of the *sella turcica*. The block appears obsolete for a series of reasons that include the lack of understanding of the mechanism of hormonal control on the evolution of the tumor, however currently obtainable with far fewer risks with systemic pharmacological drugs. Moreover, the response to common analgesics is similar (3).

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PART THREE:

SYMPTOMS

CHAPTER TWENTY-ONE

NEUROPSYCHIATRIC SYMPTOMS

CHAPTER TWENTY-ONE A

NEUROPSYCHIATRIC SYNDROMES

Patients with a cancer diagnosis have fairly characteristic responses. Initially feelings of disbelief, denial and despair prevail for several months (1) and are often followed by mood alterations, anxiety, changes in appetite, and irritability. Patients over time adapt to new life circumstances to return to a new level of normality (2). The initial psychological distress is attributable to some factors related to the disease and the patient, as well as social and cultural factors (3). The knowledge of these changes allows a better adaptation of the multidimensional treatment of the disease. Families also share the disease. Therefore pre-existing family dysfunction may worsen. Patients often continue their social life while undergoing treatment and therefore the new level of normality will have to balance with the patient's usual social setting (4). It has been reported that about 50% of hospitalized or outpatient patients (5) have diagnostic criteria for a psychiatric illness, with a prevalence of anxiety and depression (6). Some individual factors represent a risk of developing psychiatric conditions. For example, older patients exhibit a better quality of life than younger subjects, but a greater tendency to develop depression.

Assessment

The difficulty of applying the pure psychiatric approach in this context has prompted research to develop well-defined structured methods that can select the most at-risk patients, who can then be assessed more specifically to ensure a correct pathway for patients with psychosocial problems (7). The psychological screening of patients depends on the care setting. In oncology, questionnaires can allow the selection of patients at risk who require specialist support. Among these tools the Distress Thermometer (DT), the Patient Health Questionnaire for Depression, and the Hospital Anxiety and Depression Scale (HADS) are often used.

DT is a rapid tool for the evaluation of distress, understood as an unpleasant, multifactorial emotional experience of a psychological (cognitive, environmental, emotional), social, or spiritual nature that can interfere with the inevitable sharing of the disease, its physical symptoms,

and treatment (8). Distress extends from manageable feelings of vulnerability, sadness, and fear, to problems that become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crises. DS is a visual analogue scale from 0 to 10 (no distress to maximum possible distress) with a list of problems in different areas, such as the physical, emotional, spiritual, familiar, and practical. DT and the list of problems that increase the risk have been widely used in oncology, and a cut-off of ≥4 has been identified to maximize sensitivity and specificity for a given criterion, for example a psychiatric examination or other questionnaires for a psychiatric diagnosis.

Two items from the Edmonton Symptom Assessment Scale (ESAS), with a numerical scale of 0 to 10 for anxiety and depression, are considered to be a simple, well-validated tool used to identify patients to be specifically re-evaluated (9).

The most used tool for anxiety and depression is the Hospital Anxiety and Depression Scale (HADS). It has been used in palliative care and in oncology, along with the Beck Depression Inventory (BDI) and the Hamilton Depression Scale (HDS). HADS is made up of seven questions for depression and seven questions for anxiety. Each question is measured from 0 to 3 for a total of 42. A score of ≥11 is considered as equivalent to a significant degree of psychological distress (10).

HADS-anxiety (score 0-3)
1. Feeling agitated and tense
2. Frightened feeling as if something awful is about to happen
3. Worrying thoughts go through the mind
4. Sitting at ease and feeling relaxed
5.Getting frightened feeling like 'butterflies' in the stomach
6. Feeling restless as one has to be on the move
7. Getting sudden feelings of panic
HADS-Depression (score 0-3)
1.Enjoing the thinks used to enjoy
2. Laughing and seeing the funny side of things
3. Feel cheerful
4. Feeling slowed down
5. Lost interest in appearance
6. Looking forward with enjoyment to things
7. enjoying a good book or radio or TV program

Table 1. HADS questionnaire (score0-42)

Specific diseases

Some psychological alterations represent a direct response to the disease, while others are pre-existing and can be exacerbated by the stress of the disease.

Adaptation alterations are characterized by the appearance of anxiety and depression in response to an important life event that involves significant interferences on social activities, but can turn into a structured and lasting pathology. Interventions are of a psychotherapeutic nature and are aimed at facilitating adaptation to the new condition, penetrating the individual meaning of the disease for the patient and the family, clarifying the medical situation, treatments, and complications, and introducing strategies for adaptation. The decision to prescribe drugs depends on the level of distress. There are many other conditions of psychiatric interest that become difficult to manage in the context of cancer disease.

Anxiety

Anxiety can arise acutely at the time of communication of the diagnosis, related to pre-existing situations, or be exacerbated by the new situation or treatment (11). Patients may be concerned about the proposed treatment, or be anxious while waiting for a result. As the disease progresses, the anxious state often worsens even after the end of treatment, because patients believe they are more vulnerable without treatment and the presence of doctors (12).

Some medical problems can induce an anxious state, for example the use of corticosteroids. Dyspnea can mutually produce anxiety. Other causes could be the discontinuation of some substances such as benzodiazepines, alcohol, or opioids. In addition, anxiety may be associated with other diseases, such as hyperthyroidism, hypoglycemia, and some hormone-secreting tumors. Some drugs used for nausea, like neuroleptics, can produce restless stirring states, akathisia, and anxiety, which generally regress with beta-blockers or benzodiazepines. Some phobias can get worse (12). Advanced patients with young children are at risk of panic (13). Claustrophobic patients may experience panic in confined spaces during diagnostic tests or radiotherapy.

Children, if not properly prepared, can manifest anxiety and recalcitrance for painful maneuvers. Behavioral interventions, relaxation exercises, and self-distraction can be useful in these circumstances.

Post-traumatic anxiety is a specific form, caused by previous unpleasant experiences, and is relatively frequent (5-20%) (14). The

current condition can exacerbate feelings of fear. Young people with the lowest socio-cultural level are at higher risk. From the clinical point of view it presents itself with the recollection of the previous event (nightmares, restless sleep, awakening with a fixed thought) which affects the resistance to the proposed treatment as it somehow evokes the previous stressful experience. In children, play and diversion therapy are indicated. In adults, relaxation and self-suggestion techniques are suggested, up to the use of drugs to prevent and control symptoms (13).

Treatment

Psychotherapeutic interventions, such as education, training, and individual and group psychotherapy, are based on emotional support and play a fairly good part in psychological distress, even if the long-term effects have not been substantiated (15). Information and advice on the disease can be provided by the palliative team. Behavioral therapies are based on self-regulation interventions, relaxation exercises, distraction, imagination, and suggestion (16). These techniques, for example, have a certain effectiveness for anticipatory vomiting in patients who must receive chemotherapy. During existential crises, spiritual support can help the patient and family members. Typically psychotherapy is short-term and is geared to overcoming crises to assist adaptation to a new unfavorable psychological situation and facilitate patient collaboration. The inclusion of family members can be useful. Group therapies are used to orient and educate patients in forms of relaxation and to avoid isolation.

Short-acting benzodiazepines, such as alprazolam, lorazepam, and oxazepam, are the treatment of choice in acute symptoms of anxiety and panic. They are also used in sleep disorders. Clonazepam and diazepam determine a more prolonged activity. Lorazepam is preferable in patients with limited hepatic activity or using many drugs, because it is metabolized through conjugation mechanisms and then eliminated by the renal route (table 2).

Short-acting alprazolam is often used as needed for the acute control of panic situations. It can provoke rebound and its short action can facilitate the appearance of addiction.

Lorazepam has a moderately long action and is often used in anticipatory anxiety to prevent chemotherapy vomiting. Diazepam has a prolonged duration of action. Clonazepam, also long-acting, avoids rebound and is often used for panic attacks and sleep, and as an adjuvant in neuropathic pain.

These drugs can cause drowsiness, loss of memory, and dizziness, and are also associated with falls. These effects are dose-dependent, and occur especially in patients with impaired excretory organs and who use other centrally acting drugs, such as antidepressants and opioids. The withdrawal syndrome resembles that of alcohol and manifests itself with agitation, anxiety, and emotional instability. Beta-blockers can mask some vegetative effects. They can cause physical dependence, tolerance, and psychological dependence. The use of benzodiazepines should be well explained to patients, in particular for fear of addiction. Physical dependence presents itself as an acute withdrawal syndrome in patients who have received the drug for a long time. Tolerance develops with prolonged use and requires higher doses to maintain the previous effect. Patients "addicted" are those who have a clear psychological dependence that leads them to compulsively look for the drug in many ways, even unlawful.

Patients with chronic anxiety often require prolonged use. In these cases consideration should be given to the use of other atypical drugs with anxiolytic effect, such as buspirone, which has less sedative capacity. The mechanism of action is completely different. It is in fact a partial agonist of the 5-HT1A serotonin receptors and it does not interact directly with GABA receptors. The drug also works as a dopamine presynaptic D2 antagonist, as well as a partial α1 receptor agonist. Olanzapine, although belonging to the same class of benzodiazepines from a structural point of view, has a high affinity for dopamine and serotonin receptors. Another alternative is represented by the use of antidepressants, such as mirtazapine, amitriptyline, or duloxepine, to regulate sleep (17).

Benzodiazepine	equivalent dose	elimination (h)	initial dose (mg)
Clonazepam	0.25	18-50	0.25-5
Diazepam	5	30-100	2.5-5
Lorazepam	1	10-20	0.5
Alprazolam	0.5	6-20	0.25
Triazolam	0.3	1.5-5	0.125

Table 2. Comparison among benzodiazepines

Depression

The overlap of a chronic disabling disease and the symptoms of major depression is fairly well known, and is characterized by disturbances of the neurovegetative system, insomnia, fatigue, and loss of appetite and weight,

along with worsening mood, loss of hope and self-esteem, and suicidal thoughts. The diagnosis of depression in the cancer patient may be difficult because symptoms of the disease or those resulting from treatments are often similar. Mood changes, apathy, crying, loss of pleasure and daily activities, regardless of a condition of fatigue or pain, feelings of isolation and hope, and thoughts of death or suicide, are important indicators for a diagnosis.

The prevalence of depression in cancer is very similar to that found in other chronic diseases. This finding suggests the main role of the disease (18).

The lower physical capacity, the advanced state of the disease, the impact of the tumor on the quality of life, the lack of pain control, and short prognosis are strongly associated with a high prevalence of depression (19).

In this context, episodes of previous depression or a positive family history, of recurring losses, of chronic stress conditions, the use of additive substances, and low social support are other components to be considered. Some drugs, such as benzodiazepines, some hormones and chemotherapeutic agents, opioids, corticosteroids, and smoking cessation may produce symptoms of depression. Depressive symptoms can also be associated with metabolic and nutritional changes (17).

In cancer patients suicidal ideation, thoughts of death, or the inability to control their symptoms are an expression of an important depressive state. Patients at risk of suicide may be those with a worse prognosis, an advanced stage of illness, uncontrolled pain, loss of hope, personal or family history, recent losses, use of substances for abuse, and those with some types, or recently received information on the prognosis (20).

If the patient expresses suicidal ideation it is necessary to act more deeply in a specialized psychiatric environment. Maintenance of care, good communication, and encouragement of good symptom control are long-term determinants.

The state of demoralization is a syndrome distinct from existential distress. Patients describe a feeling of loss of trust, of hope, and of the meaning of life. The prevalence seems consistent, between 20% and 30% (21). These patients are at higher risk of suicide.

Treatment of depression

A prolonged and serious state of depression requires various means of psychological and pharmacological support. All antidepressants should be

used initially in low doses for a few weeks before changing their dosage (19).

Selective serotonin synaptic reuptake inhibitors (SSRIs) and mixed noradrenaline-serotonin (SNRIs) inhibitors are the most widely used and tolerated drugs compared to first generation antidepressants. Side effects are various, from the gastrointestinal to the central ones, with sensations of drowsiness, of calm, or in the form of excitatory effects. These drugs reduce appetite and therefore can cause weight loss, even if this effect is temporary.

An extension of the QT tract has been reported with the use of high doses of citalopram, for which monitoring is suggested. Antidepressants can also alter the sexual sphere. The acute suspension of SSRIs and SNRIs can produce withdrawal effects that manifest themselves in the form of anxiety, agitation, insomnia, and irritability.

In the initial choice of the antidepressant one should consider the half-life. SSRIs such as paroxetine, sertraline, citalopram, and escitalopram have a lower half-life than fluoxetine and may present a risk of withdrawal syndrome, such as with venlafaxine, which is an SNRI. The crisis can be prevented with a progressive decrease in doses or with the substitution with fluoxetine, having a prolonged half-life. On the other hand, short-term drugs have a low probability of accumulation and allow a more accurate dose titration.

Bupropion, which is primarily active on the dopaminergic system, may be useful in patients with fatigue or sleepiness, but should be used with caution in patients with high levels of anxiety. The effects on the sexual sphere are less important. It is often used in aiding smoking cessation.

Mirtazapine is an antidepressant that acts on the serotonergic system, and is most useful in patients with associated anxious states and insomnia. It has fewer gastrointestinal effects and therefore can be used in patients with nausea, and also because it improves appetite. Moreover, it induces only minor alterations of the sexual sphere.

Other antidepressants such as tricyclics and amino-dioxide inhibitors are increasingly used for central and neurovegetative effects. Psychostimulants can cause irritability, anxiety, and insomnia. They also improve mood and concentration more quickly. The pharmacological characteristics of antidepressants are described in chapter 13.

Low doses of psychostimulants (d-amphetamine, methylphenidate, modafinil) can promote a sense of well-being and better concentration, have a positive effect on fatigue, and stimulate appetite (22). These drugs, thanks to their shorter latency of action, can be useful in the advanced stages of the disease when there is not much time to wait for the effect of

traditional antidepressants. They can also enhance opioid analgesia or counter opioid-induced sedation. However, they also have important side effects, such as anxiety, insomnia, tachycardia, and emotional instability, while at high doses they can produce manic states, nightmares, and convulsions. Therefore, patients should have good cardiovascular condition and should not report arrhythmias or convulsions if they are to be prescribed these drugs.

Modafinil has been used for the treatment of narcolepsy and could be an excellent alternative for the most debilitated patients who cannot tolerate other psychostimulants.

In clinical practice a patient could start a psychostimulant drug and an antidepressant simultaneously, exploiting the immediate effect of the first and the benefits of the other during the following weeks.

The choice of an antidepressant will depend on numerous factors, such as the profile and side effects in consideration of the clinical condition and medications prescribed to the patient. Patients in whom a state of agitation and insomnia prevail may benefit from an antidepressant such as mirtazapine. Patients with cognitive impairment may benefit from drugs such as bupropion, fluoxetine, desipramine, or a psychostimulant. Patients with treatment-induced dry-mouth or urinary problems should use antidepressants with minor cholinergic effects, such as most SSRIs and SNRIs, or bupropion.

Duloxetine and amitriptyline may be useful in patients with neuropathic pain (see chapters 8 and 13). Patients treated with tamoxifen should not use CYP2D6 inhibitors, such as bupropion, and SSRIs. Venlafaxine may be considered in this case. It is important to consider whether the patient has been prescribed other serotonergic drugs.

Treatment of mood alterations, manic and bipolar states

For an acute stabilization of mood it may be useful to use atypical antipsychotics such as olanzapine or a combination of haloperidol and benzodiazepines. These drugs reduce manic symptoms and agitation in bipolar or corticosteroid-induced disorders. Valproic acid, gabapentinoids, and lamotrigine seem to be well tolerated for longer-term use. Patients receiving lithium salts should consider continuing the treatment if possible. Monitoring is critical in these sensitive patients, especially in states of dehydration. The doses of lithium will be decreased in the more advanced patients and in those who are receiving nephrotoxic drugs, like cisplatin.

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CHAPTER TWENTY-ONE B

COGNITIVE DISTURBANCES

Delirium is one of the most frequent and undervalued symptoms seen in cancer patients. It is a symptom that is remembered as a dramatic experience by the patient and family members. Delirium compromises the ability to communicate and interferes with the appropriate evaluation of symptoms, such as pain. Delirium increases the risk of hospitalization and is a negative prognostic factor for survival. In fact it is a symptom frequently reported in the last days of life and one of the most frequent indications for palliative sedation. All these elements combine such that delirium should be considered an absolute priority in terms of evaluation and treatment (1-9).

Definition and incidence

Delirium is the consequence of a dysfunction characterized by acute loss of attention and cognitive abilities without cerebral organic alterations. DSM-IV defines delirium as a disorder of consciousness, characterized by inattention, confusion, and perception disorders that develop in hours or days. It represents a mental state in which a subject appears confused, disoriented, and unable to formulate coherent thoughts and words. The incidence of delirium is quite variable depending on the setting and the disease phase, up to 90% in the most advanced stages. The underestimation of the most discrete forms also involves a significant underestimation in even the earliest stages (2). Regrettably, delirium is frequently under-recognized or misdiagnosed. This means that it is untreated or inappropriately treated. Barriers to an adequate diagnosis include a lack of consistency in utilizing diagnostic tools and confounding terminology, as well as a diversity of signs and symptoms for which it is frequently mistaken for other neuropsychiatric disorders.

In an acute palliative care unit, at admission, 25.3% and 8.2% had an MDAS (see assessment) of 7-12 and ≥13, respectively. At discharge, there was a significant decrease in the number of patients with an MDAS ≥7/30. Higher values of MDAS were associated with a lower Karnofsky status,

male gender, low level of education, less awareness of disease, more indications for end-of-life care admission, or other symptoms, hospital stay, and hospital death. Significant decreases in symptoms were observed independently of MDAS values (2). Symptom expression is amplified in patients with delirium admitted to home care or hospices, while patients without delirium can be more responsive to palliative treatments with a significant decrease in symptom intensity (10). While in patients admitted to hospice or home care program delirium in most cases worsens, as an expression of imminent death, in patients admitted into acute palliative care there are more chances of improvement (11). In the late stages of disease, delirium is also a prognostic sign, typically involving multiple medical etiologies including infection, organ failure, adverse medication effects, and, in rare situations, paraneoplastic syndromes. While only 42% of patients had delirium when admitted to a palliative care unit, 88% of patients developed it before death. Recently, 41.8% and 67.3% of patients had MDAS values ≥7 at admission and after 1 week of palliative care, respectively, confirming the tendency to a worsening in the last weeks of life (2).

Pathophysiology

There are numerous causes for the alteration of the balance of neurotransmitters that support the functioning of cognitive activity. Patients with multiple factors that can contribute to the undermining of these functions present an increased risk: factors such as age, dementia, disease, generalized inflammatory status, the consequences of chemotherapy, or the use of benzodiazepines. Besides these conditions, there are numerous precipitating factors, often present in the advanced stage of the disease (table 1) (12).

- constipation
- dehydration
- hypoglycemia
- hypoxia
- immobility
- infections
- urinary problems
- pain

Table 1. Precipitating factors

The mechanisms by which the balance of brain transmitters is interrupted is not well known. The best known theory concerns the reduction of the synaptic presence of acetylcholine, a mediator involved in attention, memory, and the state of consciousness. Dopamine and serotonin are also mediators that support attention and consciousness. The activation of dopaminergic receptors reduces the secretion of acetylcholine, while serotonin interacts with the two systems to reconcile an equilibrium. It is believed that all precipitating factors reported may reduce the formation of acetylcholine resulting in a prevalence of dopaminergic activity. Another theory insists on a model of inflammatory response, with the production of numerous substances, such as cytokines, peripherally and centrally, which operate an action on microglia which, in turn, mediates a neurotoxic dysregulation response. The microglia response is in turn under cholinergic control (13). Therefore, the two theories integrate rather than contradict (14). Cortisol may also play a role in the development of delirium. The activation of the hypothalamus–hypophyseal–adrenergic axis by the carcinogenic stress, with its inflammatory substances, would produce a release of cortisol that would act at the level of the hippocampus to induce a brain dysfunction.

Assessment

Clinical features of delirium include:

- prodromal symptoms (restlessness, anxiety, sleep disturbance, and irritability)
- rapidly fluctuating course
- reduced level of attention
- altered arousal
- increased or decreased psychomotor activity
- disturbance of the sleep-wake cycle
- emotional symptoms (lability, sadness, anger, or euphoria)
- altered perceptions (misperceptions, illusions, poorly formed delusions, and hallucinations)
- disorganized thinking and incoherent speech
- disorientation as to time, place, or person
- memory impairment (difficulty registering new material)

The nature of delirium, with its profound variability and fluctuation, makes the condition more difficult to diagnose accurately and treat effectively. The essential defining features of delirium, based on DSM-IV

criteria, constituted by an extensive list of typical symptoms and abnormalities, have been focused on the most essential concepts of disordered attention and cognitive disturbance. The importance of acute onset, fluctuating course, and organic etiology are still recognized as relevant elements. Altered psychomotor activity and behavior, perceptual disturbances, and delusions are not essential for the diagnosis of delirium and seem to be not necessarily associated with this phenomenon. Thus, delirium is better conceptualized as "a disorder of arousal and cognition" (15), to be distinguished by dementia, where no arousal disturbances are present. Indeed, a disorder of the arousal system with altered levels of consciousness and impaired attention seems to be a pathognomonic sign of delirium.

- Temporal factors Rapid development (hours-days) Fluctuation - Existential symptoms Disorders of consciousness (from hyperattention to coma) Disturbances of attention - Cognitive disorders: Temporo-spatial disorientation Mnemonic difficulties Difficulty in language (reading, writing, speech) Disorganization of thought and incoherent expressions Visual or auditory misperceptions Disappointment - Other symptoms Alteration of the sleep-wake rhythm Psychomotor symptoms with agitation

Table 2. Clinical manifestations of delirium

Subtypes of Delirium

The arousal disturbance is the basis for classifying delirium into several subtypes. These include the hyperactive subtype (agitated), the hypoactive subtype (hypoaroused), and a mixed subtype with alternating features (16, 17). The hyperactive subtype is more frequently

characterized by hallucinations, delusions, agitation, and disorientation. On the contrary, hypoactive delirium is more characterized by confusion and sedation (18). The majority of forms (67%) are either of the hypoactive or mixed subtype, while agitated delirium, which is more familiar to clinicians, actually occurs in a minority of cases (16-18).

The clinical features and symptoms of delirium may overlap those of other psychiatric disorders, including depression, mania, psychosis, or dementia. The hypoactive subtype is often initially misdiagnosed as depression. The onset and temporal sequencing of depressive and cognitive symptoms may be particularly helpful to differentiate delirium from depression, particularly in the context of advanced disease. Moreover, the level of cognitive impairment is more severe and abrupt in onset than that which occurs with depression. Finally, arousal disturbance is not typical of depression. The hyperactive or mixed subtypes could mimic a maniac episode. The temporal onset, the course of symptoms, and the presence of an arousal disturbance associated with cognitive impairment, may help in differentiating these disorders. The presence of hallucinations and delusions in hyperactive forms must be distinguished from a variety of psychotic disorders. The disturbance in consciousness or arousal associated with memory impairment and disorientation favor a diagnosis of delirium, as these features are not present in other psychotic disorders. Visual and tactile hallucinations predominate in delirium, while in schizophrenia auditory hallucinations prevail. The context of advanced medical illness makes delirium a more likely diagnosis.

Differentiation with dementia is challenging. Both delirium and dementia share many points, including cognitive impairment, impaired memory, disordered thinking, limited judgment, and disorientation. However, in dementia the patient is alert and does not present disturbances of consciousness or arousal. Also the typology of onset may help. In dementia, symptom onset is subacute and progressive, and the sleep-wake cycle is less disrupted. Short- and long-term memory deficits, impaired judgment, reduced capacity for abstract thinking, and alterations in higher cortical functions (aphasia and apraxia) are more prominent than in delirium.

Differently from dementia, delirium may be a reversible process, if the identifiable cause is removed. However, delirium may not be reversible in the last weeks of life, due to irreversible processes including multiple organ failure (3).

Assessment

Numerous scales or tools have been developed for the screening of a cognitive impairment or the establishing of a diagnosis of delirium. The most helpful to clinicians are the Mini-Mental State Examination (MMSE) and other delirium diagnostic and severity rating scales, including the Delirium Rating Scale (DRS), the Confusion Assessment Method (CAM), and the Memorial Delirium Assessment Scale (MDAS). These tools are briefly described in the subsections below.

a) The MMSE is useful in screening for cognitive failure. MMSE provides a quantitative assessment of the patient's cognitive performance and capacity, measuring the severity of cognitive impairment (19). The MMSE assesses five general cognitive areas: orientation, registration, attention/calculation, delayed recall, and language. Traditionally, a score of 24-30 indicates no impairment, whereas a score of 18-23 indicates mild impairment, and a score of 0-17 represents a severe impairment. However, it does not distinguish between delirium and dementia.

b) The DRS is a 10-item clinician-rated symptom rating scale for diagnosing delirium (20). The scale is designed to identify delirium and distinguish it from dementia or other neuropsychiatric disorders. Each item is scored by choosing the best rating, which has a numerical weight designed to distinguish the characteristics of delirium. A score of 12 or greater is positive for delirium.

c) The CAM is a nine-item delirium diagnostic scale, which can be administered rapidly using a simplified diagnostic algorithm that includes only four items (21). The four items include an acute onset and a fluctuating course with inattention, and either disorganized thinking or an altered level of consciousness.

d) The MDAS is a 10-item (score from 0 to 3) assessment tool validated among hospitalized patients with advanced cancer (22). Other than being a good delirium diagnostic screening tool, MDAS is a reliable tool for assessing delirium severity. A cutoff score of 7 out of 30 yielded the highest sensitivity (98%) and specificity (76%) for a delirium diagnosis in a palliative care population. The MDAS has advantages over other delirium tools in that it is both a diagnostic and a severity measure ideal for repeated assessments and for treatment intervention trials (table 3).

Awareness
Disorientation
Short-term memory impairment
Impaired digit span
Reduced ability to maintain and shift attention
Disorganized thinking
Perceptual disturbances
Delusions
Decreased or increased psychomotor activity
Sleep-wake cycle disturbance (disorder of arousal)

Table 3. Items from the MDAS

Assessment of Etiologies of Delirium

The first step to managing delirium is gaining knowledge of the etiologies, correction of the contributing factors, and management of symptoms. The optimal outcome would be a patient who is awake, cognitively intact, alert, calm, not agitated, and able to communicate coherently with family and staff. Unfortunately, in the last days-weeks of life, the treatment of delirium is quite complex and often fails in achieving the desired clinical outcome. Diagnostic studies should be performed if a clinically suspected etiology may be readily identified with minimal use of invasive procedures and effectively treated with simple interventions that minimize risk and limit distress to the patient. A diagnostic evaluation includes an assessment of potentially reversible causes of delirium (table 4). Sepsis, dehydration, or major organ failure should be investigated, as well as medications potentially contributing to delirium being identified. Metabolic abnormalities including hypercalcemia, hypoxia, or disseminated intravascular coagulation may cause delirium. Imaging studies of the brain or cerebrospinal fluid examination may be appropriate in some instances. The etiology is discovered in less than 50% of advanced cancer patients presenting delirium, and frequently the identifiable cause is irreversible or difficult to treat (1). Thus, diagnostic work-up is often limited by either practical constraints such as the setting (home, hospice) or the focus on patient comfort, such that unpleasant or painful diagnostic procedures are avoided.

However, in earlier stages of advanced cancer, investigations are potentially helpful in many cases (4, 8), as a specific treatment may be able to reverse delirium, with an improvement in 50% of cases (4). The most frequent reversible causes of delirium are dehydration and adverse

effects of drugs, including opioids, whereas hypoxic and metabolic encephalopathies are less likely to be reversible in terminal delirium.

In advanced cancer patients, delirium may be due either to direct effects on the central nervous system or some indirect effects of disease or actual treatments (4, 23). Advanced cancer patients are more vulnerable to the development of delirium with drugs acting on the central nervous system, including opioids, chemotherapeutic agents such as methotrexate, fluorouracil, vincristine, vinblastine, bleomycin, carmustine cisplatin, asparaginase procarbazin, and ifosfamide, as well as immunotherapeutic agents like interleukin-2 and interferon, and glucocorticosteroids (24, 25, 27).

Brain tumor and brain metastases
Seizures
Metabolic encephalopathy due to organ failure
Electrolyte abnormalities
Chemotherapy, immunotherapy
Radiation
Hematological abnormalities
Paraneoplastic syndrome
Steroids
Opioids
Anticholinergics, antiemetics, antivirals

Table 4. Causes of delirium in advanced cancer patients

Management of delirium

a) Nonpharmacologic Interventions

Other than identifying and correcting the etiologies of delirium, symptomatic therapies are important (6, 28, 29, 20, 30), as they may be the only interventions in a dying patient. Maintaining fluid and electrolyte balance, providing nutrition, supplementing vitamins, reducing anxiety and disorientation, and continuing comforting, reassuring interactions with family members may be helpful. A quiet environment, in a room with familiar objects, a visible clock or calendar, and the presence of relatives will provide comfort. Judicious use of physical restraints or one-to-one nursing observation is beneficial when necessary. Interventions focusing on reorientation, correction of hearing and visual impairment, reversal of dehydration, and early mobilization may be beneficial.

b) Pharmacologic Interventions

Specific treatments alone are frequently ineffective in managing symptoms of delirium, and the use of psychoactive drugs may be necessary (table 5). Anti-dopaminergic drugs such as some neuroleptics, other than being utilized as antiemetics, seem to be the first choice for the management of delirium. Haloperidol in low doses (1 to 3 mg/d) is usually effective in targeting agitation and hallucinations (31, 32). Doses can be titrated upward to relieve target symptoms (33, 34). An intravenous route facilitates rapid onset of action. If intravenous access is unavailable, a subcutaneous route of administration may be used and switched to oral administration when possible. Parenteral doses are approximately twice as potent as oral doses (7, 35).

The addition of parenteral lorazepam may be helpful (36, 37), providing more effective sedation for the agitated patient and minimizing extrapyramidal side effects associated with haloperidol (37). Alternately, a switch to a more sedating neuroleptic such as chlorpromazine has been proposed. Lorazepam, alone, seems to be ineffective and may worsen cognitive impairment (38). The combination of haloperidol and chlorpromazine in low doses is highly effective in managing symptoms of delirium while improving cognitive function in both subtypes, i.e., hypoactive and hyperactive (38). Methotrimeprazine, a molecule similar to chlorpromazine, is often utilized parenterally (intravenously or by subcutaneous infusion) to control confusion and agitation in terminal delirium (38). Hypotension and excessive sedation are potential limitations of this drug. Methotrimeprazine seems to offer some analgesic properties, through nonopioid mechanisms (39).

Neuroleptics	
- Haloperidol	1-5 mg every six hours
- Chlorpromazine	10-50 mg every six hours
- Methotrimeprazine	12.5-50 mg every six hours
- Dehydrobenzoperidol	1-2.5 mg every six hours
Atypical neuroleptics	
- Olanzapine	2.5-20mg every 12 hours
- Risperidone	1-3 mg every 12 hours

Benzodiazepines	
- Lorazepam	0.5-2 mg every six hours
- Midazolam	30-60 mg/24 hours (by continuous infusion)

Table 5. Medications used to manage delirium

Atypical antipsychotic agents with less risk of extrapyramidal side effects include clozapine, risperidone, and olanzapine (40, 41). Olanzapine proved highly effective in advanced cancer patients with delirium. Delirium resolved in most patients, without reporting extrapyramidal side effects. Older age, dementia, and hypoactive delirium subtype are associated with a poor response to olanzapine. Sedation is the most common side effect. The principal limitation of the use of atypical neuroleptics is the lack of availability in parenteral formulations.

While these drugs may reduce agitation, clearing the sensorium, and improving cognition, this clinical target may not be achievable in the last days of life, as processes causing delirium may be persistent and irreversible during this phase. These patients will often necessitate a treatment that decreases the level of consciousness. Irreversible delirium that is unresponsive to standard neuroleptics in the last days of life is the principal indication to start palliative sedation (see chapter 26) (42-43).

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CHAPTER TWENTY-ONE C

SLEEP DISTURBANCES

Sleep abnormalities are quite frequent in cancer patients, regardless of the stage of the disease, and are reported in 25-95% of patients (1-3). Regrettably, this problem is often overlooked. These disorders can occur during certain phases, often attributed to anxiety and depression, and presumably considered self-resolving.

Sleep abnormalities have been classified into six main categories, of which insomnia is probably the most frequent in the population diagnosed with cancer (4), with a prevalence twice that of the general population (5).

Insomnia
Breathing alteration
Hypersomnia
Alteration of the circadian rhythm
Parasomnias
Movements

Table 1. Classification of sleep disorders

Insomnia can be defined as the difficulty of falling asleep, periods awake at night, early awakening in the morning, and changes in daytime capacity. Insomnia can appear alone or be associated with a triggering condition. From the temporal point of view insomnia is considered transitory (<1 month), short term (1-6 months), or chronic (> 6 months). The general criteria for a diagnosis of insomnia are shown in table 2 (6).

- Difficulty to start or maintain sleep, early awakening, non-restorative sleep - Difficulty falling asleep despite favorable environmental conditions - At least a symptom of fatigue, reduced attention, mood alterations, daytime sleepiness, energy reduction, errors at work or driving, feeling of tension and headache, worry related to sleep

Table 2. General criteria for a diagnosis of insomnia

In some tumors the prevalence is higher, as in the case of breast cancer, in which insomnia and fatigue prevail, while in lung cancer nocturnal awakening due to respiratory problems is more frequent (6).

Pathophysiology

The sleep cycle is divided into phases of sleep with rapid eye movement (REM) and not (NREM), subdivided into electroencephalographic subgroups. The substantial difference lies in the fact that in the REM phase, sleep is restorative and characterized by the presence of dreams accompanied by vegetative phenomena, while in the NREM phase muscle paralysis prevails. Muscle paralysis is mediated by the activation of inhibitory circuits (7). In a normal nocturnal sleep, a fluctuating progression between the two phases is observed. Some changes in sleep can modify these phases in a specific way, as in the case of disturbances induced by respiratory changes for the REM phase (8).

Mechanisms by which cancer causes sleep disorders are unspecified. It is claimed that psychological, behavioral, and physical phenomena carry out a multifactorial intervention. The most accredited hypothesis is based on various factors, such as susceptibility to insomnia, precipitating factors, and perpetual factors (table 3) (9).

Individual predisposing factors, such as age, for example, are difficult to modify. Specific precipitating factors may be related to the disease, treatment, or other associated phenomena. For example, pain, urinary disorders, the use of opioids, anxiety, and depression, are invariably associated with sleep disorders. The same generalized inflammatory state, characterized by the production of cytokines, is considered an important cause, often associated with fatigue and anorexia (6).

Predisposing Factors	Precipitating Factors	Perpetual Factors
psychiatric disorders	delirium	habits
female gender	pain	mismatch to
age		insomnia
familiarity	mutilating interventions	unrealistic
culture	hospitalization	expectation
	radiation therapy	
	other pathologies	
	(urinary symptoms)	
	drugs (opioids)	
	marrow transplantation	

Table 3. Etiological factors in insomnia in the cancer patient

Assessment

Considering that sleep disorders often go unnoticed, it is necessary in the first instance to make the phenomenon visible and obtain the necessary information, retracing the individual predisposing factors and the possible recognizable reversible causes. There are standard questionnaires, such as the Pittsburgh sleep quality index (PSQI) that measures the quality and profile of sleep, taking into consideration the quality, latency, duration, efficiency, use of drugs, and the consequences in the daytime hours (10).

While with the Edmonton Assessment Scale, insomnia is assessed simply with a value of 0 to 10 as a single item, the Athens Insomnia Scale (AIS) is a particularly useful tool. Eight factors are measured, of which 5 are based on nocturnal sleep and 3 on the resulting daily dysfunctions. A cut-off of ≥ 6 establishes a diagnosis of insomnia (11) (table 4). Other specialized measurements, such as EEG or actigraphy, are generally not performed in a palliative setting.

Sleep induction	0: No	1: Slightly delayed	2: Fairly delayed	3: Very late
Night awakenings problem	0: No	1: Minor problem	2: Major problem	3: Serious
Awakening	0: Not early	1: A little before	2: Fairly anticipated	3: Strongly anticipated
Sleep duration	0: Sufficient	1: Mildly insufficient	2: Fairly insufficient	3: Poorly insufficient
Sleep quality	0: Satisfactory	1: Mildly Unsatisfactory	2: Fairly unsatisfactory	3: Very unsatisfactory
Wellness	0: Normal	1: Mildly decreased	2: Fairly decreased	3: Very decreased
Functional capacity	0: Normal	1: Mildly decreased	2: Strongly decreased	3: Very decreased
Drowsiness	0: No	1: Mild	2: Considerable	3: Intense

Table 4. Athens insomnia scale

Treatment

Sleep disorders greatly affect the quality of life of cancer patients. Symptoms such as fatigue, impaired daytime function, and mood changes, frequently reported, may be caused by sleep disorders. Therefore, treatment requires a multimodal approach with pharmacological interventions and not for a lasting effect over time.

- *Non-pharmacological interventions.*

Many studies have shown the effectiveness of cognitive behavioral treatment (12). There are recommendations on sleep hygiene measures (table 5). The best effects are achieved on sleep latency, quality, and duration. Complementary interventions include muscle relaxation, hypnosis, and regular exercise.

Keep schedules constant
Use relaxation techniques (hot bath, music) before going to bed
Create a peaceful, silent, dark environment
Use comfortable cushions and mattresses
Use the bed only for sleeping
Finish eating 2-3 hours before sleep
Physical exercise to be completed at least 2-3 hours before going to sleep
Avoid the use of stimulants (caffeine, tea, coca), nicotine, alcohol

Table 5. Sleep hygiene measures

-Pharmacological interventions

Treatment with hypnotic drugs is largely used for sleep disorders. Benzodiazepines interact on GABA receptors, increasing chlorine conductance and maintaining a neuronal hyperpolarization state. The global effects are a depression of neuronal activity, with amnesia and hypnosis, with loss of sleep latency. Benzodiazepines have different pharmacokinetic characteristics and the choice is based particularly on drugs with a short half-life to avoid prolonged tails of the effect, especially in the elderly. Use should be cautious due to the disorientating effects, due to the inhibition of structures with inhibitory activities, especially in fragile individuals (table 6).

Antidepressants have sedative properties and in patients with depressive notes they can facilitate sleep.

Short duration	Triazolam	0.125 mg	rapid induction, less effect on duration
	Alprazolam	0.5-1 mg	medium duration
	Lorazepam	0.5-2 mg	induction and maintenance, possible tail
Long duration	Diazepam	5-10 mg	slow induction, accumulation, daytime sedation
	Clonazepam	0.5-2 mg	long-lasting
	Amitriptyline	25-100 mg	sedation risk
	Duloxepine	25-100 mg	
	Mirtazapine	15-30 mg	
	Olanzapine	5-10 mg	
	Haloperidol	1-5 mg	

Table 6. Drugs used to facilitate sleep

However, antidepressants have various side effects (see chapter 13), especially anticholinergic, which must be taken into account in the general economy. Mirtazapine could be an interesting option for its effects on various neuromediators. Melatonin regulates the circadian cycle by acting on the hypothalamus. Its use in insomnia is controversial (6).

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CHAPTER TWENTY-TWO

GASTROINTESTINAL SYMPTOMS

CHAPTER TWENTY-TWO A

DIARRHEA

The pathophysiology of the intestinal tract is quite complex. In fact, intestinal function is mediated by a strict relationship between endocrine, paracrine, and neurogenic activity. The gastrointestinal tract is endowed with an intrinsic nervous system, the myenteric and submucosal plexus, which receives an extrinsic control from the central nervous system through the vegetative system. Furthermore, the gastrointestinal tract has its own pace-marker that generates an autonomous electrical activity. The segmental contractions that produce peristaltic contractions, which mix and push the luminal content, are the result of these complex interactions. Many transmitters mediate these activities. Any damage of any origin in cancer patients at various levels of this complex system results in changes in motility and gastrointestinal function.

Diarrhea is quite frequent in cancer patients (5-10%). It is considered a major complication for patients undergoing chemotherapy (1) and belongs to the ten most frequent consequences of drug reactions (2). Diarrhea is generally defined as a frequent passage of stools urgently, generally more than three evacuations per day. It is commonly diagnosed when the total weight of the feces and their quantity of water, and the number of evacuations increase, often accompanied by urgency, perianal discomfort, or incontinence, as a consequence of the incomplete absorption from the luminal content (3). The most common causes of diarrhea are presented in table 1.

The consequences are very serious. The loss of fluids, salts, and albumin, hyponutrition, a decline in immunological function, risks of infection, and skin lesion are significant problems. Beyond this, diarrhea requires major care efforts, in addition to precipitating patients into despair. Moreover, it represents a further cost of a chemotherapy treatment because it requires prolonged hospitalizations (4).

Pathophysiology

From a pathophysiological point of view, many mechanisms can produce diarrhea and very often overlap.

- ***Osmotic diarrhea***

The ingestion of poorly absorbable solutes that modify the osmolarity of the luminal content induces osmotic diarrhea. The proximal part of the intestine is highly permeable to water, and already in the duodenum the sodium is absorbed to adjust the osmolarity of the content with respect to the plasma, eventually returning water to the intestinal contents. On the contrary, the mucous membrane of the ileum and the colon has a low permeability to sodium and solutes. An efficient active transport allows the reabsorption of electrolytes and water also against different electrochemical gradients (3).

The use of laxatives or magnesium-containing antacids causes diarrhea. When high doses of lactulose, a non-absorbable sugar, are introduced, the compensating capacities of the colon bacteria responsible for metabolization are overcome, and diarrhea is produced, proportional to the osmotic capacity of the unabsorbed saccharide (5). In a similar way, all carbohydrates poorly absorbed due to digestive difficulties induce a diarrhea characterized by a low pH, due to the presence of short chain fatty acids, a high content of carbohydrates, a high osmolarity, and flatulence. In some cases 5-fluoruracil may induce a digestive deficit of lactase further reducing the tolerability to chemotherapy (6). Other substances, such as magnesium, sulfates, and other little absorbable salts, can produce diarrhea, although in this case the fecal pH will not be acidic. Broad-spectrum antibiotic treatment can reduce the bacterial flora that has a protective metabolic function, resulting in diarrhea (5). Generally, osmotic diarrhea is self-limiting with the suspension of causative agents.

- ***Secretory diarrhea***

Secretory diarrhea frequently overlaps with other mechanisms (3). It is associated with an alteration of ion transport in intestinal cells, with a reduction in absorption functions or an increase in secretory activity. In this case the anionic gap is smaller and the quantity of nutrients is irrelevant to the qualities of the diarrhea, which therefore persists even under fasting. Many factors can influence ion transport in the intestine. These include bacterial toxins, secretagogues, such as bile acids or laxatives, and circulating secretagogues, such as some hormones, drugs, or poisons. Furthermore, some anatomical-functional problems can

compromise the regulation of intestinal function by limiting the absorption surface (due to illness or intestinal resection (7). Endocrine tumors, such as carcinoid tumors, cause diarrhea releasing neurotransmitter secretagogues such as serotonin and substance P (8). In Zollinger-Ellison syndrome, diarrhea is the consequence of elevated circulating gastrin levels, whereas in medullary thyroid carcinoma, circulating calcitonin increases intestinal secretion (3). Malabsorption phenomena can cause secretive diarrhea (3). Diarrhea induced by chemotherapeutic agents, such as fluoropyrimidine, taxanes, capecitabine, and irinotecan (4), graft versus host disease (GVHD) (10), and targeted therapies involve serious treatment problems and often lead to prolonged discontinuation of treatment (1). Diarrhea is a significant consequence of the treatment for colon cancer (9). These drugs cause damage to the intestinal mucosa, with necrosis and extensive inflammation of the wall. Following the release of inflammatory substances, a secretion of fluids and electrolytes is produced in the intestine. Similar changes occur in patients with GVHD or postradiotherapy enteritis (10, 11). Chronic post-radiotherapy enteritis is less common and is associated with high doses, generally above 45 Gy. In this case a state of endoarteritis with intestinal ischemia is likely to prevail as a mechanism (9). On the other hand, intestinal mucositis facilitates over-infection by opportunistic pathogens, such as Clostridium difficile, Clostridium perfringens, Bacillus cereus, Giardia lamblia, Cryptosporidium, Salmonella, Shigella, Campylobacter, and Rotavirus, especially in particularly immunosuppressed patients. Bacterial toxins induce intestinal secretions through nerve reflexes mediated by neuroendocrine cells or inflammation (12). The use of long-term antibiotics, such as ampicillin, clindamycin, or cephalosporins is associated with diarrhea in operated or immunosuppressed patients, as a consequence of the alteration of bacterial flora and the growth of new pathogens (13). Diarrhea may be due to food mixtures used for enteral nutrition, due to the osmolarity of the mixture, the rate of infusion, or possible contamination (9). Finally, many drugs, such as diuretics, antacids, and laxatives, can produce diarrhea through an activation of cellular secretory mechanisms (4).

- ***Motility disorders***

Changes in intestinal motility may reduce the contact time between the luminal content and intestinal cells. This occurs mainly after extensive surgical procedures, such as gastrectomy, intestinal resections, including the ileocecal valve, and some concomitant chronic diseases, such as

diabetes (14). Spinal cord lesions can reduce intestinal mobility and promote the growth of intestinal bacteria that de-conjugate bile acids (15).

Drugs
Infections
Endocrine tumors
Malabsorption
Chemotherapy
Radiotherapy
Concurrent diseases

Table 1. Principal causes of diarrhea

Assessment

Assessment is based on medical and surgical history, drug review, physical examination, and description of stool characteristics. When the stools are firm, watery or fat, clear, bloodless, or contain indigested fragments, it is likely that the problem affects the small intestine or the proximal part of the colon. Frequent diarrhea with small amounts of stool, dark, which contains mucus or blood, and which passes with a sense of urgency, is likely to recognize its problem in the lower part of the colon or in the rectum. Diffuse inflammation can produce the two forms described (3).

Recovery time is quite important. While osmotic diarrhea often decreases with fasting or the withdrawal of the offending drug, secretory diarrhea lasts several days, sometimes weeks, as in the case of severe gastrointestinal chemotherapy toxicity. Actinic colitis is typically to be attributed to a previous radiation treatment. A physical exam must precede any subsequent step. Signs of anemia, fever, hypotension, lymphadenomegaly, hepatosplenomegaly, ascites, abdominal distension, deterioration of nutritional status, a reduction in anal sphincter tone, a rectal mass, or a fecal impact are essential elements in directing to a causal diagnosis. Procedures such as gastrectomy, intestinal resections including the ileocecal valve, some concomitant chronic diseases such as diabetes (14), and medullary lesions can reduce intestinal mobility and promote the growth of intestinal bacteria that de-conjugate bile acids (15).

Toxicity	0	1	2	3	4
		<4 stools/day	>4-6	7-10	>10
					or nocturnal stools
	-	moderate cramps	severe	bleeding	need of parenteral support
Patients with colostomy					
	0	small increase	moderate increase	large increase	need of intensive care

Table 2. Grading diarrhea

Some elements are fairly straightforward and point to the probable etiology. Carbohydrate malabsorption, for example, is associated with foul odor and gelatinous stools, while an intermittency between diarrhea and constipation is quite typical of diabetic neuropathy, irritable bowel syndrome, or intestinal obstruction. Vegetative neuropathy or anal sphincter dysfunction is characterized by nocturnal diarrhea. Fecal impacts can produce an apparent diarrhea because the liquids pass through a partial obstruction or the bacteria, favored by the states, ferment the fecal material. Symptoms of rapid emptying following gastric resection, such as early nausea, abdominal distension, weakness, and postprandial diarrhea followed by hypoglycemia, sweating, and tachycardia, are quite typical. Secretory diarrhea associated with gastrointestinal symptoms from peptic disease is suggestive for gastrin secreting cancer. High levels of circulating serotonin cause other effects beyond diarrhea, such as hypotension, sweating, heat, and palpitation (3, 13). The association with heat intolerance, palpitation, and weight loss suggests probable hypothyroidism. In elderly patients, intestinal ischemia can be suspected from diffuse atherosclerotic disease. Rectal examination and abdominal palpation can help to evaluate fecal masses and exclude a fecal impact, or anal lesions.

The assessment of the sites of disease allows us to refine the picture. In this case, imaging studies may be appropriate according to the diagnostic suspicion. Laboratory tests will complete the overall assessment. If possible, the feces will be collected to undergo a qualitative examination. The presence of leukocytes suggests an exudative mechanism, such as in actinic or infectious enteritis. Positivity for bacteria, fungi, or viruses has obvious therapeutic consequences (16). An anionic gap >50 mmol/L due to a reduction in the content of sodium and potassium content in the feces

suggests an osmotic diarrhea, while lower values (<50 mmol per L) indicate a secretory diarrhea from the active secretion of salts and water .

- Steatorrhea - Weight loss, weakness, fatigue (caloric deprivation) - Glossitis (folate deficiency and vitamin B12) - Hyperkeratosis, bruising, hematuria (vitamin A and K deficiency) - Weakness, paresthesia, tetany (calcium and magnesium deficiency) - Premature nausea, abdominal distension, weakness, postprandial diarrhea followed by hypoglycemia, sweating, malaise, and tachycardia (after gastric resection) - Osteopenia and bone pain (vitamin D and calcium deficiency) - Chyloid ascites, peripheral edema (abnormal lymphatic transport) - Peripheral neuropathy (vitamin B12 deficiency) - Anemia (iron deficiency, folate, vitamin B12)

Table 2. Signs and causes of malabsorption

- ***Treatment***

The use of drugs believed to be responsible or contributing to the appearance of diarrhea should be suspended, while applying simple and practicable dietary advice such as avoiding foods with gluten, cold foods, high-fiber vegetables, food rich in fat, coffee, or alcohol. Oral hydration enriched with simple salts and sugars is essential. Intravenous hydration is often necessary, especially for patients with nausea and vomiting or with symptoms of significant dehydration.

Given the complex mechanisms examined, there are no widely accepted protocols. Common sense suggestions for some specific etiologies should be followed. Cholestyramine, aspirin, and sucralfate have been successfully used in actinic enteritis (17), although the best treatment is based on prevention, applying the most advanced radiation protective protocols (18). Amifosphine reduces the incidence of 5-fluorouracil diarrhea, although its use may be associated with hypotension (19).

Steroids can have a positive effect under various conditions, including secretory diarrhea, intestinal pseudo-obstruction, actinic enteritis, and endocrine tumors, due to the ability to reduce the production of inflammatory mediators and to promote water absorption. They have also been used in diarrhea associated with GVHD (16).

Antibiotics, such as amoxicillin and norfloxacin, are useful in the treatment of intestinal bacterial diarrhea (20), while in some cases they

will be suspended because of diarrhea, as in the case of pseudo membranous enteritis, in which, vice versa, metronidazole must be administered (21). Probiotic bacteria, which survive intestinal passage, can repair the bacteria-free intestinal environment (22), for example in actinic enteritis. Alkalinization of the intestinal tract and the use of absorbents, activated charcoal, and neomycin are promising methods to prevent delayed diarrhea with irinotecan, without affecting the blood concentrations of irinotecan and its active metabolites (23-26).

- All conditions	Hydration, dietary advice
- Radiotherapy diarrhea	Hypofractionated radiotherapy, amifosfin, cholestyramine, aspirin, sucralfate, silicate, corticosteroids
-Bacterial growth	Antibiotics
- Associated with antibiotic therapy	Discontinuation of antibiotics, metronidazole, probiotics
- Chemotherapy diarrhea	Alkalization, loperamide, octreotide
- Endocrine gastrointestinal tumors	Octreotide
- Diabetic Diarrhea	Clonidine

Table 3. Etiologic treatments

Opioids have traditionally been used for their antidiarrheal properties, thanks to the widespread presence of opioid receptors in the gastrointestinal tract, at the level of the smooth muscle and the myenteric plexus, and at the spinal level. It is well known that their activation increases the tone of the ileocecal valve and decreases the peristalsis in the ileum and the colon. It also reduces the defecation reflex by inhibiting anorectal sphincter relaxation and decreasing the rectal sensitivity to distention. As a consequence, the contact time between the intestinal mucosa and the lumen content increases, thus promoting a greater absorption of water and electrolytes (3). Among the opioids, the most specific effect is observed with loperamide, due to the inability of this substance to pass the hemato-cerebral barrier and the consequent exclusive peripheral action. The standard dose of loperamide is 4 mg, followed by 2 mg after each stool. The dose is titrated to clinical effect up to 12 mg/day (26). The combination with simethicone is also more effective in forms with gaseous intestinal distension (27). The risk of determining a paralytic ileus should always be taken into account.

Numerous studies have reported the efficacy of octreotide in the forms of refractory diarrhea (26, 28). The mechanism of action of octreotide is

multifactorial, as it reduces the secretion of numerous pancreatic and intestinal hormones, increasing intestinal transit time and increasing the absorption of electrolytes (29). Octreotide has been effective in many clinical conditions, such as carcinoid tumors, VIPoma, gastritis, lung tumors, AIDS, GVHD, actinic enteritis (30-32). Hormonal responses do not always correspond to the clinical response. The response seems to be dose-dependent (30). The doses used ranged from 0.3 mg to 1.2 mg/day. The slow-release formulation (30 mg per month) was evaluated for the prevention and treatment of diarrhea during subsequent cycles of chemotherapy (33). However, no efficacy was observed in preventing diarrhea during pelvic radiant therapy, emphasizing the differences between prevention and treatment (10, 32).

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CHAPTER TWENTY-TWO B

CONSTIPATION

Constipation is a fairly common and debilitating symptom in cancer patients. The prevalence is quite wide, and depends on the stage of the disease or the type of tumor (1).

It is difficult to provide a clear definition, in relation to the different meaning and above all to the individual variability that prevents the identification of clear ranges of normality. Clinically, the symptoms most easily associated with constipation are difficulty in eliminating feces, stool consistency, and a reduced frequency of defecation. In patients with advanced cancer, the combination of disease and medication dramatically increases the prevalence of constipation, especially in the elderly, in a range of 10-70%, depending on the study setting and the type of patients examined (2-4). Constipation, assessed by bowel function index (BFI) has been found in approximately two-thirds of advanced cancer patients (BFI >28). After one week of palliative care, BFI decreased. Indeed, in patients with a BFI of ≤28 there was a significant worsening of constipation. In patients with a BFI of >28 at T0 there was a significant increase in the use of laxatives. In patients with an initial lower BFI of ≤28 that worsened in the following week, there was a lower use of laxatives. Dehydration and the use of benzodiazepines were independently associated with higher BFI scores. Thus, patients with normal bowel function at initial assessment may worsen in their condition a week later due to lack of prevention or subsequent under-treatment (5). Despite its high prevalence, constipation is often underestimated and receives attention only to its presentation. Intestinal function is often linked to the private sphere and is not always openly discussed. Therefore, only a professional approach can limit the embarrassment for patients. In addition to causing discomfort, constipation influences daily activities, appetite, and socialization, thus compromising quality of life. Synergism with other abdominal problems, such as ascites or an abdominal mass, can increase abdominal pain and, by limiting diaphragmatic excursions, favor the appearance of dyspnea (3).

Pathophysiology

For an understanding of the phenomenon it is necessary to know the main intestinal functions. The propulsive forces in the colon are called mass movements, appear 3-5 times a day, usually upon awakening or after a meal, and are characterized by peristaltic waves beginning in the transverse colon and pushing the endoluminal contents towards the rectum. About 10 liters pass in the small intestine. These products come in large part from the gastrointestinal tract and partially from the fluids introduced with the diet. Of this quantity, only 0.5-1 liter will reach the large intestine due to the high ileal absorption, and only a minimal amount will be absorbed in the colon, proportional to the time when the fluids are in contact with the colic surface. The rectum fills up as a result of mass movements. The distension of the intestinal wall stimulates the distension receptors inducing the reflex of defecation with an increase in the contraction of its wall. The voluntary contraction of the diaphragm and the abdominal muscles further increases the pressure, thus facilitating the evacuation (3). The anal canal has an internal sphincter and an external sphincter. The internal sphincter is composed of smooth muscles and has an autonomous control, while the external sphincter is composed of striated musculature and is controlled voluntarily, so that it is possible to facilitate or delay the time of defecation.

Causes and clinical features

The causes of constipation are often multifactorial in cancer patients (table 1). Constipation can be secondary to concomitant systemic diseases, or caused by the tumor or the treatment performed. In addition there are many substances that can induce constipation, of which the most known class is represented by opioids. Constipation is frequently associated with neurological changes, such as visceral neuropathies. The involvement of extrinsic innervation involves the loss of the inhibitory activity of the circular muscles of the colon, and a decrease in the release of acetylcholine.

Constipation is associated with other symptoms such as anorexia, nausea, and early satiety to determine a complex syndrome named vegetative dysautonomia, also characterized by postural hypotension and tachycardia. Other factors may contribute to this syndrome, such as diabetes, some drugs, such as vinca-alkaloids, some antidepressants and opioids, malnutrition, and decreased physical activity (3).

Ogilvie syndrome, also known as pseudobstruction, describes some states characterized by an intrinsic defect in the smooth intestinal muscles, with colonic dilatation in the absence of mechanical obstruction. These clinical conditions, where damage of the submucosal structures and myenteric plexus prevails, may be due to metabolic alterations, neurological diseases, non-surgical traumas, inflammatory processes, infections, tumors, radiation therapy, drugs, cardiovascular diseases, and lymphoid infiltrates (3).

Many of the same causes described above can produce a denervation that can abolish the functioning of the pelvic floor, observable for example after chemotherapy, radiotherapy, compression or cancer invasion, or prolonged opioid administration without adequate monitoring. Loss of rectal muscle tone is often a consequence of prolonged inactivity of particularly debilitated patients. The rectal sensation can be reduced after treatment with vincristine or invasion of the sacral nerves. The rectum-sigmoid junction is a key area for the mechanisms of constipation. The inability to coordinate pubo-rectal muscles and sphincter is frequently found in various diseases. Anism is a spastic form of the pelvic floor, known as rectosphinter dis-synergia for its similarity to vesicoureteral dis-synergia. An overlapping extrinsic innervation has been observed that explains the association of urinary and rectal symptoms. The integrity of the spinal cord is essential to ensure coordination of these fine muscle activities. In patients with a lesion beyond the lumbosacral area, incontinence is controlled but not defecation. The reason is related to the interruption of the cortical pathways, confirming the importance of a supraspinal control. Moreover, the response to a meal is reduced. An appropriate stimulus may still be sufficient. In patients with cauda equina injury, transit time is prolonged and the rectal reflex is deficient, so the protection against incontinence is severely compromised. In patients with Parkinson's disease, constipation is probably caused by the vegetative dysautonomia of the myenteric plexus. Psychiatric illnesses are often associated with intestinal dismobility (6). Many metabolic alterations predispose to constipation, in particular intense states of dehydration. Finally, many drugs are able, with various mechanisms, to reduce intestinal transit (table 1) (7).

One feature of chronic opioid use is the constancy of constipation. Opioid receptors are well distributed at intestinal level, and their activation reduces overall intestinal transit. Opioids increase intestinal tone and non-propulsive motility, and decrease intestinal secretion, probably through tryptaminergic neurons operating in the myenteric plexus and the release of noradrenaline, which antagonizes intestinal secretory mechanisms,

regulated by α2-adrenergic receptors. Opioids also reduce the release of the vasointestinal peptide (VIP), which is a powerful secretagogue and an inhibitor of smooth muscle contraction.

The same extension of the transit can facilitate the reabsorption of water and electrolytes. Opioids can produce excessive feces consolidation, as well as other gastrointestinal symptoms (8). While most side effects of opioids tend to shrink spontaneously over time, constipation tends to persist, probably as a result of other contributory factors, such as reduced activity, de-hydration, diet, use of other drugs, or disease. It is estimated that in patients receiving opioids, there is a prevalence of more than 70% (4), even if there is no true correlation with the dosage (9).

Primary constipation (due to non cancer or habits)
- Age
- Reduced mobility
- Fluid and nutrient reduction
- Lower fiber diet
- Previous abdominal surgery
- Increased fluid loss
- Alterations of cognitive status
- Depression
- Reluctance to assessment
- Poor privacy
- Weakness

Secondary constipation (due to factors related to cancer disease)
- Direct tumor (obstruction)
- Peripheral nerve involvement (gangliopathies, dysautonomic neuropathies due to radiotherapy or chemotherapy)
- Neurological diseases (Parkinson's, brain tumors, spinal tumors)
- Weakness
- Metabolic alterations (dehydration, hypokalemia, hypercalcemia, hypothyroidism, pheocromocytoma)
- Ascites

Iatrogenic constipation
- Opioids
- Anti-inflammatory drugs
- Chemotherapy
- Anticholinergic drugs
- Antiemetics

- Aluminum salts
- Diuretics
- Iron
- Anticonvulsants
- Vinca-alkaloids
- Antiserotonergic drugs

Table 1. Causes of constipation

Assessment

The definition of constipation is particularly difficult due to the enormous individual variability. It is therefore essential to understand what the patient intends for constipation, quantity, frequency, difficulty in evacuating, and sense of incompleteness (3). In general it is defined as a decrease in the frequency of evacuations with feces that are difficult to eliminate (2). A frequency of three evacuations per week is considered a standard of normality, with any individual variables. Various tools have been developed to measure constipation. The "Rome II criteria", used in the general population, is based on six elements: the effort, the hardness, the feeling of incompleteness, anorectal obstruction, less than three evacuations a week, and two weeks a year with more than two signs of these. The Bowel Function Index (BFI), more commonly used in palliative care and opioid constipation, is based on three simple elements, evaluated in the last week, on a scale from 0 to 10: ease of evacuation, sense of incompleteness, and general judgement on intestinal activity (10). It has been found that a BFI threshold of $\geq$28 discriminates constipated from non-constipated patients (11). The Victoria Hospice Bowel Performance Scale uses images to describe the consistency of feces and is easily understood (12). The Patient Assessment Constipation Symptoms consist of three elements – abdominal symptoms, rectal symptoms, fecal signs – and is validated for opioid-induced constipation (13).

The causes of constipation should be ascertained through consideration of the clinical history and the examination of the patient. In particular, the habits of intestinal transit and its variations over time, the use of laxatives, drugs used, the type of food, and the environmental conditions need be considered. The examination includes the evaluation of abdominal distension and the presence of palpable masses, and the auscultation of intestinal noises, possibly accompanied by a rectal examination to detect the presence of fecal symptoms and to highlight anal lesions. Patients with supra-sacral spinal cord lesions may have a reduced sensation but a still

functioning sphincter, unlike patients with sacral involvement. A radiological study is sometimes necessary if there is doubt regarding a state of intestinal obstruction or to visualize the presence of abundant fecal material along the intestinal tract, possibly corroborated by the administration of barium. To study the transit time, radiographs of small pieces of radiolucent tubes followed along the intestinal axis can be helpful. On this basis, a score has been proposed regarding the amount of feces along the abdominal quadrants (14), even if there is no exact correlation (15). The metabolic alterations must be evaluated with appropriate laboratory tests.

Treatment

In recent years, recommendations have been produced, from which the limits of evidence are evidenced above (12, 16). In general they suggest to synergize the main mechanisms considered and the targeted pharmacological intervention. For this reason it is essential to recognize the cause underlying the phenomenon.

Treatment should include general measures and specific treatments. The metabolic alterations and the use of some drugs can be easily identified and corrected, and a good hydration can promote an improvement (3). Fiber deficiency in the diet is hardly correctable for practical reasons in an advanced patient. A favorable environment and discrete privacy can encourage inspiration in a hospital environment.

However, some conditions are irreversible, especially in the advanced stage of the disease, when the patient is debilitated and treated with necessary drugs such as opioids. Prophylactic treatment with laxatives is necessary in these patients.

In the presence of an ampoule filled with hard stools, a manual removal, possibly assisted by an appropriate sedation, will be necessary. More proximal masses can be minced with an endoscope and a water-filled enema. These interventions must be considered for an acute treatment. The ordinary measures provide for the use of laxatives given chronically (14). Laxatives work with different mechanisms and are often used in combination to strengthen their effect in the most resistant cases. Clinical response, acceptability, and patient preference should orient the choice (see table 2).

Drugs	onset (days, hours)	Notes
Lubricants-mineral oils - liquid paraffin 10 mL/d	1-3 days	Inhalation of paraffin
Detergent laxatives - Docusate 300 mg	1-3 days	Never together with mineral oils
Mass agents - Wheat	4-8 days	To be taken with plenty of water, risk of fecal impact
- Methylcellulose, ispaghula	4 days	
Osmotic laxatives - Lactulose 15 mL b.i.d.	1-2 days	Cramps, gaseous distension, useful in hepatic encephalopathy
- Mannitol - Sorbitol - Polyethylene glycol 25 ml x 2		To be combined with high volumes of water
Salt laxatives - Magnesium salts - Sodium salts		1-6 h Not in renal failure
Stimulating laxatives - Senna 15 mg - Dantron 50 mg - Polyphenols - Bisacodyl 10 mg - Sodium picosulfate 5 mg	6-12 h	Colic pain Pink urine Colic pain
Opioid antagonists	4-6 h	Withdrawal syndrome

Table 2. Categories of laxatives, onset, and usage-related notes

Laxatives are categorized according to their mechanism of action. There is no data that can guide the first choice. The combination lactulose-senna seems to be the most effective, while among them it is difficult to establish the best efficacy (15). Docusate, however, despite its traditional use, seems to offer little effectiveness (16).

Mass agents contain polysaccharides or cellulose resistant to the aggression of intestinal bacteria. They promote the formation of fecal mass, but also require large quantities of water to avoid the formation of overly hard stools.

Emollient laxatives are non-absorbable surfactant substances, with stimulating and secretagogue activity. They are the most used and probably most effective drugs, and are represented by anthraquinone derivatives, such as senna, cascara and dantron, and diphenylmethane derivatives, such as bisacodyl and phenolphthalein. They act at the level of the colon and the distal ileum, directly stimulating the myenteric plexus. Senna is converted into the active form by colon bacteria. Dantron and polyphenols undergo to glucurono-conjugation and are secreted in the bile (15). The enterohepatic circulation multiplies the action. Bisacodyl stimulates myenteric plexus structures producing contractions at the level of the colon, and decreasing the absorption of water. All of these drugs can induce cramp pain. Bisacodyl suppositories promote colonic peristalsis with a short latency due to the rapid conversion to the active metabolite thanks to the rectal flora.

Lubricating laxatives are represented by mineral oils used to lubricate feces and generally are used in tight and resistant constipation to unblock the situation, rather than as a chronic treatment.

Lubiprostone is a laxative that acts with a mechanism quite different from the previous ones, activating the chlorine channels. This effect produces peristaltic and secretive activity (17).

Osmotic agents are not attacked or absorbed in the intestine and draw water into the intestinal lumen. In this way the feces soften. Lactulose increases the weight of the stool but can cause cramping pains and flatulence, following bacterial metabolism at the level of the colon. On the other hand, macrogol is not metabolized by bacterial flora (18). Macrogol hydrates hardened stool, increases the volume, and decreases the duration of intestinal transit. Effectiveness does not diminish over time (19). Amidotrizoate is effective and safe in forms resistant to laxatives and is used when necessary, with an efficacy obtainable in 6-8 hours (20).

Salt laxatives, whose main ingredients are magnesium, sulfate, and phosphate, exert an osmotic effect, increasing the volume of luminal water and peristalsis. The effect appears in a few hours. Their use can lead to significant electrolyte alterations, such as magnesium accumulation in renal failure, or hypernatremia. Administered rectally, they activate peristalsis in 15 minutes. Repeated use of enemas may cause hypokalemia and hyperphosphatemia or rectal gangrene in patients with hemorrhoids. Rectal glycerine has an osmotic and lubricating action.

Metoclopramide appears to be effective in forms induced by opioids both by central antidopaminergic action and by cholinergic action (3). Neostigmine, a potent pro-cholinergic, has been proposed for refractory constipation to laxatives (21).

Opioid-induced constipation may be particularly refractory to conventional laxatives. Naloxone is a competitive antagonist on central and peripheral opioid receptors. Oral bioavailability is very low (<2%) for the extended hepatic conjugation metabolism, with production of active or inactive metabolites (6β-naloxol and glucuronide). Therefore, oral administration could provide selective intestinal antagonism without reducing the central effects of opioids, especially analgesia, unless metabolic saturation is exceeded. In the first studies, naloxone was shown to revert opioid-induced constipation at 20% doses of morphine (22), although withdrawal symptoms (yawning, sweating, shivering) appeared in about a third of patients (23). The dose of naloxone selected was generally dependent on the dose of morphine administered. But the response appears to be proportional to the tolerance level achieved rather than the dose itself, and the risk of a systemic withdrawal syndrome remains well established. The slow-release association of oxycodone and naloxone with a ratio of 2:1 (see chapter 19b) has allowed improvement in the performance of the antagonist avoiding the possibility of overcoming the liver's metabolism capabilities for a slower absorption of the traditional naloxone up to 40-80 mg every 12 hours (24). Many studies have confirmed the efficacy of the combination in reducing opioid-induced constipation without altering analgesia, at least at the recommended doses (25). At higher dose there is the risk of a reduced analgesia due to the absorption of naloxone in plasma concentrations able to pass the blood-brain barrier.

Methylnaltrexone is an exclusively peripheral antagonist, and therefore not able to interfere with central analgesia, thanks to poor cerebral penetration. Administered every two days at a dose of 0.15 mg/kg subcutaneously, it induced an evacuation within a few hours (26, 27). Ineffectiveness has been reported in about half of the patients. This finding is compatible with all antagonists where there are many other causes of constipation (28). PEGylated derivative of naloxone, thanks to the pegilation, results in an antagonist that does not pass the hematocerebral barrier effectively. In doses of 25 mg/day, it determines a predominantly peripheral effect resulting in an increase in intestinal transit velocity in patients receiving opioids without interfering with analgesia (29). Naldemedine, an orally available peripherally acting μ-opioid receptor antagonist, in doses of 0.2 mg/day, showed in phase III trials more efficacy than placebo at increasing the frequency of bowel movements in patients with constipation induced by opioid treatment for cancer pain or chronic non-cancer pain (30).

In some cases, modification of opioid therapy may improve constipation (31). There seems to be a specificity of opioids in the ability to produce constipation. For example, methadone, buprenorphine, and fentanyl, very lipophilic molecules, tend to produce less constipation than morphine and hydroxymorphone, probably due to a less insistent receptor distribution on the gastrointestinal area, and to activity at low plasma concentrations. These pharmacokinetic attitudes make certain drugs concentrate less in the intestinal receptors. These phenomena have been found clinically in the switching to methadone and fentanyl (3). Theoretically, opioid switching for less constipation capacity, such as to tapentadol due to the partial opioid component or the oxycodone-naloxone combination, could improve the clinical picture. Similarly, substitution of the oral and parenteral routes could have advantages, even if these aspects have not yet been well studied (32).

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CHAPTER TWENTY-TWO C

NAUSEA AND VOMITING

Nausea has been defined as an unpleasant sensory and emotional experience that is described as a "sick" feeling with or without a sense of impending vomiting or retching. Nausea is also associated with a perception of epigastric or upper abdominal unpleasantness or awareness (1).

Severe nausea, vomiting, or retching are disabling symptoms and may lead to significant adverse effects including dehydration, electrolyte imbalances, malnutrition, and significant deterioration in quality of life.

Nausea and vomiting become more common in the advanced stage of disease, and have been found to be predictors of a shortened survival (2), with 71% of patients presenting nausea in the last week of life (3). Nausea can be ascribed to the primary disease or the side effects of therapy, be secondary to debilitation, and be caused by an unrelated comorbid condition for non-medical conditions, including significant advanced cardiac and obstructive pulmonary disease, end-stage renal disease, and advanced dementia (4). In older patients, comorbidities such as mesenteric ischemia, subacute cholangitis, Meniere's disease, myocardial infarction, drug toxicity, constipation, and urinary tract infection may produce gastrointestinal symptoms, such as nausea and vomiting. Environmental stimuli, such as sights, sounds, or smells, may initiate nausea (5). Moreover, nausea and/or vomiting can be induced by increased intracranial pressure, chemotherapy, medications like opioids, radiation, movement, hypovolemia, pain and anxiety, or headache.

The most relevant causes for nausea/vomiting in cancer patients include chemotherapy-induced nausea/vomiting (CINV), opioid-induced nausea and vomiting, and radiation-induced emesis (RIE).

Nausea assessment

Assessment

Various instruments are available for the assessment of cancer-related nausea, vomiting, and retching (6). Many of them were designed to focus

on the patient's more broad functional status or quality-of-life issues. The Index of Nausea, Vomiting, and Retching (INVR) for example, has questions regarding the number of retching episodes in the previous 12 hours and the distress felt due to these episodes. The INVR utilizes a 5-point Likert type scale and has been found to be clinically useful and easy for patients to understand, although it was not as sensitive to early changes as the visual analogue score (6).

The Hesketh score assesses the acute emetogenic potential of individual chemotherapeutic agents (7). Agents are classified according to the proportion of patients expected to develop emesis with each agent in the absence of an antiemetic prophylaxis: level 1, <10% of patients; level 2, 10-30% of patients; level 3, 30-60% of patients; level 4, 60-90% of patients; and level 5, >90% of patients.

In the Edmonton Symptom Assessment Scale, nausea is commonly measured on a scale of 0-10 (8). Episodes of vomiting, however, are not considered.

- ***Chemotherapy-induced nausea and vomiting (CINV)***

The development of CINV is a devastating consequence of cancer treatment, and these gastrointestinal symptoms are the most feared effects of chemotherapy. Despite advances in antiemetic therapy, 55% of patients receiving emetogenic chemotherapy (e.g., cisplatin) experience nausea or vomiting (9). Of interest, despite standardized treatments and evidence-based guidelines (10), regrettably, 57% of patients administered cisplatin and 36% of patients administered doxorubicin or cyclophosphamide are often not treated according to the guidelines (11). Patients with nausea and vomiting induced by chemotherapy after moderately emetogenic chemotherapy experience a significantly negative impact on their health-related quality of life (HRQOL) (12). Chemotherapy can induce acute or delayed nausea/vomiting. Delayed emesis is commonly considered as an event that begins or persists for more than 24 hours after chemotherapy. Highly emetogenic therapy may produce a biphasic pattern of emesis, starting 2-3 hours after chemotherapy, peaking at roughly 6-8 hours, and persisting for 10-12 hours following chemotherapy. Delayed emesis develops in a large number of patients (40-90%), occurring 18-24 hours post-chemotherapy, peaking at roughly 48-72 hours, and subsiding only after 48 hours. Thus, the management of highly emetogenic chemotherapy should be considered over a five-day period. Moderately emetogenic chemotherapy induces emesis 6-12 hours post-chemotherapy, peaking at

about 24 hours, and subsiding 24-36 hours after the administration of chemotherapy (13).

High emetogenic risk	Cisplatin Cyclophosphamide Mechorethamine Streptozocin
Moderate emetogenic risk (30-90%)	Carboplatin Cytarabine Doxorubicin Epirubicin Daunorubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin

Table 1. Agents with high and moderate emetogenic risk

The specific mechanisms involved in CINV for most drugs are not fully understood. It is likely there are multiple direct and indirect mechanisms by which drugs may produce nausea and vomiting. CINV seems the result of different activities mediated by drugs. The pathophysiology of nausea is not clearly understood. Nausea may be caused by an activation at a lower intensity of the same systems as vomiting (table 2). Because of the different and complex aspects of CINV prevention and treatment, monotherapy is often insufficient, requiring additional, and often multiple therapeutic approaches to manage this common side effect.

- Direct or indirect stimulation of abdominal vagal and abdominal splanchic nerve afferents that project to the chemoreceptor trigger zone (CTZ), nucleus tractus solitarius of the vagal nerve, and directly to the vomiting (or emesis) center. This activation can result from a direct activation of superficial receptors, or indirectly through other activities, for example changes in gastrointestinal motility, distension, and toxic damage to gastrointestinal mucosa (14). Serotonin (5HT) release from mucosal enteroendocrine cells is the primary mediator of vagal and splanchic nerve stimulation. The release of substance P and cholecystokinin may also play a role. Serotonin release is enhanced by

several neuromediators such as acetylcholine (M_3), norepinephrine (beta), 5HT ($5HT_3$), and histamine (H_1) receptors. Activation of these pathways can also result from medication-related toxicity producing pathologic effects on the visceral organs or dysmotility. Drugs could also directly activate the chemoreceptor trigger zone (CTZ) in the area postrema of the fourth ventricle. CTZ activation may also occur indirectly by releasing substances from the gastrointestinal tract. The CTZ contains dopamine (D_2), histamine (H_1), and acetylcholine (M_1) neurokinin-1, mu opioid, gaba-aminobutyric acid (GABA), N-methyl d-aspartate (NMDA), and serotonin ($5HT_3$) receptors (3).

- Activation of the vomiting center through the poorly understood central nervous system stimuli. The role of the central nervous system is likely predominant when CINV is due to unpleasant medication taste or smell as well as anticipatory nausea and vomiting (15).
- Activation of vestibular inputs, primarily mediated through H1 and M1 receptors, to the vomiting center results in nausea and emesis.
- Medications may directly act on the nucleus tractus solitarius and/or vomiting center through activation of 5-HT_3 H_1, and M_1 receptors, or indirectly through other neurotransmitters such as Substance P (16).

Table 2. Different mechanisms for nausea and vomiting induced by toxic agents

- ***Radiation-induced emesis (RIE)***

Radiation-induced emesis (RIE) can occur early (30 minutes to 4 hours after a radiotherapy session) and can be prolonged for 2-3 days in up to 40% of patients. When RIE is severe enough it can lead to an interruption in the treatment schedule (17, 18). The proposed mechanisms of RIE include a direct and indirect stimulation of CTZ, the stimulation of gastrointestinal mucosa nerves, the release of neurotransmitters, direct or indirect stimulation of various receptors, cortical or vestibular mechanisms, or release of emetic mediators from the tumor area. Serotonin seems to play a crucial role in RIE via stimulation of 5-HT3 receptors and in the vagus nerve, greater splanchnic nerves, and CTZ (19). Irradiation activates 5-HT3 receptors on the terminals of abdominal vagal nerves thereby stimulating afferent emetic input to the nucleus tractus solitarius, leading to increased c-Fos immunoreactivity with subsequent nausea/vomiting (20).

- ***Drug-induced nausea and vomiting***

Many drugs may induce nausea and vomiting. Adrenergic agents, such as β-agonists, generally delay gastric emptying, whereas beta-blockers enhance gastric emptying. Clonidine, an α_2 agonist, may induce nausea and vomiting. Anticholinergic agents, such as some tricyclic antidepressants, inhibit contractile activity and delay gastric emptying. Dopamine agonists, opioids, digitalis, and chemotherapeutic agents such as cisplatin remain the major offenders. Non-steroidal anti-inflammatory drugs (NSAIDs) may induce nausea and vomiting by damaging gastric mucosa and activating peripheral ascending impulses. A central effect of alcohol on the CTZ has been recognized, besides the well-known consequence of damage to the gastric mucosa (8, 21). Nausea and vomiting are common side effects from opioid therapy, occurring in over 60% of patients (22). Opioids have central and peripheral actions. The mechanisms which may contribute to opioid-induced nausea/vomiting include the stimulation of the emetic center via D_2 receptors of the CTZ, richly distributed in the area postrema, a direct opioid receptor stimulation, and increased vestibular sensitivity. In addition, they peripherally induce a relevant delay in gastric emptying and in intestinal transit. Nausea occurs when there is relaxation of the esophageal sphincter tone, delayed gastric emptying, and poor duodenum motility. Narcotic bowel syndrome is characterized by a picture similar to pseudo-obstruction. This problem prevalently occurs during the initial period of administration of opioids, as tolerance tends to develop after some days. These aspects are comprehensively reported in chapter 19b.

- ***Disorders affecting the central nervous system***

Various neurological diseases may produce a disturbance in central control of intestinal motility, resulting in gastrointestinal syndromes, such as vomiting or intestinal pseudo-obstruction with or without gastric stasis.

Neurological lesions at the spinal cord, above T5, may isolate the spinal sympathetic control from the influence of high centers. This results in a delayed gastric emptying and delay in duodenal progression. Initially, there is a severe gastric stasis with dilatation and ileus. When the loss of function is stabilized, patients who develop quadriplegia are more likely to have intestinal complications than those with paraplegia. The incidence of gastroesophageal reflux is increased and gastric emptying impaired. Chronic constipation may reinforce the clinical picture facilitating the development of nausea and vomiting. (23).

- ***Autonomic failure***

Autonomic failure is more frequently observable in advanced cancer patients with poor performance status and is often associated with anorexia-cachexia syndrome (see chapter 23a). The mechanisms are multifactorial, including tumor invasion of nervous tissue, malnutrition, damage from chemotherapy or radiotherapy, concomitant drugs, and preexisting diseases. Substantially it is a sort of paraneoplastic syndrome, producing gastroparesis (8).

Other neurological disorders may affect the extrinsic gastrointestinal innervation. For example, the vagal autonomic neuropathy in diabetic patients may be responsible for gastric motor disturbances with gastroparesis. Motility disorders may also involve the upper small bowel, due to delayed gastric emptying. Peripheral neuropathies, manifestations of autonomic neuropathy, with bladder dysfunction, sweat disorder, orthostatic hypotension, impotence, nephropathy, and retinopathy are frequently found, as gastroparesis is commonly reported in patients with longstanding, insulin-dependent poorly controlled diabetes (21). Neurological diseases, such as dystrophia myotonica and progressive muscular dystrophy, amyloidosis, collagen vascular diseases, and autoimmune neurological diseases, may affect parietal structures of the gastrointestinal tract, inducing motility dysfunction, which can precipitate nausea and vomiting. Radiation injury is another important cause of gastrointestinal dysmotility. Early vomiting is probably due to direct mucosal injury, whereas late vomiting and gastrointestinal stasis may be related to radiation-induced inflammation or strictures.

- ***Metabolic disorders***

Significant gastrointestinal alterations may be associated with thyroid and parathyroid diseases. Intestinal pseudo-obstruction may develop both in hyperthyroidism and hypothyroidism. The role of gastrointestinal hormones in upper intestinal motility disorders is still unclear (24).

Management

The management of nausea and vomiting should be directed at a specific cause. Removing the offending agents and correcting etiologies that may induce these symptoms should constitute the initial therapeutic effort. If the cause of nausea/vomiting is known, targeted therapy is consequential. However, in most circumstances it is unclear which receptors are contributing to a specific clinical condition. Multiple etiologies as well as multiple receptor sites may contribute to nausea

and/or vomiting. Thus, a single drug antiemetic therapy cannot provide a complete effective solution in most circumstances. The use of combination therapy and/or a multimodal approach may improve efficacy over monotherapy (8, 21).

Different drug classes have antiemetic activities, including anticholinergics, antihistamines, sedative/anxiolytics, butyrophenones, phenothiazines, other anti-dopaminergics, 5-HT3 receptor antagonists, and corticosteroids. Antiemetic agents which are effective for nausea and vomiting induced by multiple different stimuli may be referred to as broad spectrum antiemetic agents, while drugs that are effective for nausea and vomiting induced by one specific type of stimulus may be referred to as narrow spectrum antiemetics. Some medications which may be effective as prophylactic antiemetics may not be effective for the treatment of nausea and/or vomiting. Moreover, some drugs may inhibit emesis but not effectively improve nausea and vice versa, while other agents are effective for both nausea and vomiting. The response to single drugs may differ with various specific etiologies. For example, an effective antiemetic for acute chemotherapy-induced emesis may not be effective for the treatment of motion sickness or opioid-induced nausea. The relative affinities of antiemetics to receptors are reported in table 3.

Phenothiazines antagonize dopaminergic D2 receptors in the CTZ. Heterocyclic phenothiazines (e.g., prochlorperazine) exhibit more potent antiemetic activity and less sedation than chlorpromazine and promethazine, but their use is associated with a higher incidence of extrapyramidal side effects (e.g., tardive dyskinesia, akathisia, acute dystonia, pseudo parkinsonism). Additional side effects include dry mouth and hypotension.

Butyrophenones used for nausea/vomiting are droperidol and haloperidol. These agents act by antagonizing dopaminergic D2 receptors at the CTZ and have an anti-alpha adrenergic activity. The most common side effects include hypotension, restlessness, anxiety, dysphoria, sedation, and extrapyramidal symptoms. Droperidol produces a prolongation of the QT interval on the electrocardiogram

	DA2	H1	M1	5HT2A	5HT3A	5HT3B	5HT3C	5HT4	NK1	Cb1
Scop		+	+++							
Dyph		+++	++							
Prome	++	+++	+++							
Hydr		+++	++							
Proc	+++	++	++	+						
Levo	+++	+++	+++	+++						
Halo	+++	+		+						
Meto	+++					++		++		
Onda						+++				
Gran					+++	+++	+++			
Dola					++	+++				
Palo					+++					
Apre									+++	
Dron										+++
Mirta	+	+	+++		+					
Olan	+	+	. +	+++						

Table 3. Relative affinities of antiemetics to various receptors. Scop=Scopolamine, Dyph=Dyphenhidramine, Prom=Promethazine, Hydr=Hydroxyzine, Proc=Prochlorperazine . Levo=Levopromazine, Halo=Haloperidol, Meto=Metoclopramide , Onda=Ondasetron, Gran=Granisetron, Dola=Dolasetron, Palo=Palosetron, Apre=Aprepitant, Dron=Dronabinol, Mirt =Mirtazapine, Olan= Olanzapine

The most commonly used drug for nausea/vomiting is metoclopramide for its prokinetic gastrointestinal properties, which antagonize dopaminergic D2 receptors at the CTZ and peripheral D2 receptors in the gut. Metoclopramide increases lower esophageal sphincter tone, thus favoring the gastric emptying. Extrapyramidal symptoms generally occur at higher doses.

Antihistamines (e.g., hydroxyzine) antagonize M1 acetylcholine receptors in the vestigular system and histamine H1 receptors. Common side effects are dry mouth, sedation, blurred vision, and urinary retention.

Benzodiazepines (e.g., lorazepam) have been used to reduce anticipatory nausea and vomiting that may occur before chemotherapy (13). This treatment should possibly be associated with behavioral treatments as well.

Corticosteroids are very effective in combination with setron agents, but less impressive as monotherapy. Although corticosteroids such as dexamethasone are well-established antiemetics for chemotherapy-induced nausea and vomiting, the mechanism of steroid-induced antiemesis

remains uncertain. It seems that this class of drugs reduces the levels of arachidonic acid metabolites that may be emetic. Alternately, they can inhibit the release of hypothalamic prostaglandin synthesis, with tryptophan depletion, can diminish brain levels of serotonin and endorphin release, or may produce psychological effects or "membrane-stabilizing" effects (25). The onset for reasonable antiemetic effects is usually about 4-5 hours.

The setron drugs (5HT3 receptor antagonists) are relatively effective and broad spectrum antiemetics that block 5HT3 receptors both centrally and peripherally. The 5HT3 receptor antagonists have a chemical structure that is similar to serotonin. These agents are well absorbed after oral administration and cross the blood-brain barrier. The setrons are largely metabolized in the liver and have no significant interactions with cytochrome P450 enzyme inducers/inhibitors. Generally, there is no need to alter dosing in renal insufficiency with conventional dosing. Palonosetron exhibits a strong binding affinity to the 5HT3 receptor and a long-plasma elimination half-life and provides effective antiemetic activity for delayed CINV and or multiple chemotherapy regimens (25).

5HT3 receptor antagonists ("setrons") exhibit a favorable side effect profile, as they lack the unwanted sedative, extrapyramidal, behavioral, and cardiovascular side effects of other antiemetics. Headache, lightheadedness and dizziness are the most uncommon side effects (26). High dose setron therapy could slow down intestinal transit, potentially leading to constipation and/or abdominal pain, bloating, or cramping. Acute asymptomatic, reversible, dose dependent prolongation of the PQ, QRS, and QTc intervals have been reported. The granisetron transdermal system may be a possible and comfortable solution.

NK1 receptor antagonists have been ultimately added as an option aimed at treating nausea/vomiting. The antiemetic activity of NK1 receptor antagonists is largely or entirely from their central action (27).

Tetrahydrocannabinol (THC) has been reported to be more effective than placebo in preventing chemotherapy-induced nausea and vomiting. The mechanism via which cannabinoids may produce antiemetic effects remains uncertain. It has been hypothesized that there is an effect on the modulation of gastric motility, direct effects on cannabinoid receptors located within the "emetic neural circuitry", or perhaps by blocking the effects of tumor necrosis factor to amplify vagal afferent responsiveness, by suppressing neurotransmission by downregulating ryanodine channels through a protein kinase A (PKA)-dependent mechanism (28). At the present time cannabinoids are not recommended as first-line agents for the treatment or prevention of CINV or other nausea and vomiting states, but

might be reserved for patients with intractable nausea and vomiting unresponsive to other therapies or as rescue for unresponsive breakthrough nausea and vomiting (29).

Practical recommendations for emesis from chemotherapy

Recommendations for the prophylaxis of acute and delayed nausea and vomiting induced by multiple-day chemotherapy, high-dose chemotherapy, and breakthrough nausea and vomiting have been produced by different societies.

Emetic risk category	Antiemetic regimen,
Highly emetogenic	Dexamethasone 5-HT3 receptor antagonist, Aprepitant Olanzapine
Moderately emetogenic	Dexamethasone 5-HT3 receptor antagonist
Low risk	Dexamethasone
Minimal risk	No routine prophylaxis recommended

Table 4. Recommended treatment regimens for prevention of chemotherapy-induced nausea and vomiting

For patients receiving high-dose chemotherapy with stem cell transplant, a combination of a 5-HT_3 receptor antagonist with dexamethasone and aprepitant (125 mg orally on day 1 and 80 mg orally on days 2 to 4) is recommended before chemotherapy (30). For patients undergoing multiple-day chemotherapy-induced nausea and vomiting, a regimen with a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant, is recommended before chemotherapy for the prophylaxis of acute emesis and delayed emesis. In patients experiencing breakthrough nausea and vomiting, the use of 10 mg oral olanzapine, daily for 3 days, is recommended. Mild to moderate sedation in this patient population (especially elderly patients) is a potential problem with this agent. For the prevention of nausea and vomiting following moderately emetogenic chemotherapy, for example in carboplatin-treated patients, it has been

shown that the addition of an NK1 receptor antagonist to dexamethasone and a 5-HT3 receptor antagonist provides a moderate benefit. The role of NK1 receptor antagonist is unclear for patients receiving oxaliplatin. There is no specific 5-HT3 receptor antagonist of choice for the prevention of acute emesis. No routine prophylaxis for delayed emesis is recommended, unless when using drugs known to have a potential for delayed emesis, such as oxaliplatin, doxorubicin, and cyclophosphamide, for which the use of dexamethasone for 2-3 days could be considered (31). For patients receiving low emetogenic chemotherapy, a single drug such as dexamethasone, a 5-HT3 receptor antagonist or a dopamine receptor antagonist may be used. No antiemetic should be administered for delayed nausea. Patients who have other concomitant risk factors for emesis should be properly assessed (32).

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CHAPTER TWENTY-TWO D

MALIGNANT INTESTINAL OBSTRUCTION

Intestinal obstruction is a major complication in patients with abdominal or pelvic malignancies. Although it may occur in all phases of the disease, it predominantly develops in the advanced stages with a variable incidence, according to the study setting, between 5 and 40%, especially in ovarian and colon cancer (1, 2).

Physiopathology

In the presence of an obstacle, the intestinal smooth muscles continue to contract upstream increasing peristaltic activity, feeding a vicious circle represented by distension–secretion–hyperactivity, and a worsening of the clinical picture. The endoluminal hypertensive status is maintained by an inflammatory response and a release of prostaglandins and vasoactive intestinal polypeptide (VIP). Consequently, there is a production of hyperemia and edema of the intestinal wall, with an accumulation of fluids in the lumen. An alteration of the local and neuro-hormonal self-regulating mechanisms of the splanchnic flux spike the evolution towards multiple organ failure caused by hypotension, with tachycardia, reduction of venous pressure, and accumulation of blood in the splanchnic district. It follows a renal failure due to the reduction of the filtrate and severe state of dehydration.

Increased abdominal distension reduces venous return further and compromises ventilation for diaphragm elevation. Fluids and electrolytes are sequestered inside the lumen for intense vasodilation. Sepsis is consequent to intestinal microperforations and the passage of intestinal bacteria into the circulation (2).

Clinical presentation

The primary tumor, the recurrence of disease after surgery, radiotherapy or chemotherapy, and widespread carcinomatosis represent the most common causes of intestinal obstruction. Tumor grown,

abdominal masses, fibrosis, and adhesions produce an extrinsic narrow intestinal lumen occlusion, while polypoid lesions and stenosing constrictions can cause intestinal endoluminal occlusion. Neoplastic linitis, due to infiltration of the muscular structures, produces a stiffening of the intestinal wall causing an intramural obstruction. Some neuromuscular dysfunctions of the wall attributable to neurological alterations, such as in diabetes or some paraneoplastic forms, determine an alteration of motility without creating a real mechanical obstruction which is functional. Moreover, constipation, when induced by opioids or other drugs, can favor the occlusive state in the presence of disease (1).

The clinical presentation depends on the level of obstruction, which often involves more levels, as in the case of carcinomatosis. In most cases there is a progression from the partial obstruction, in which the symptoms are more nuanced, to the complete one. Pelvic tumors, for example, can produce the most insidious and slow onset forms, with alternating periods of subocclusion and a fair abdominal distension. With the highest occlusions, for example at duodenojejunal level, as in pancreatic tumors or with tumors infiltrating the small intestine, distension can be minimal and intestinal symptoms occur early. The evolution of clinical events is variable, from a few days to weeks.

Prognostic factors

The evolution of the symptomatology depends on the rapidity of evaluation of the disease and the impact of the treatment (table 1). Obstruction due to extension of cancer disease is commonly associated with poor survival.

Carcinomatosis
Ascites
Low performance status – Weight loss
Re-obstruction

Table 1. Negative prognostic factors for surgery

In fact, surgical attempts present a remarkable morbidity and mortality, around 20% and 40%, respectively, and success in resolving the symptoms is quite variable (3, 4). Besides the obstruction, carcinomatosis can cause

motility problems for the intestinal paralysis due to the involvement of the neuromuscular structures of the intestinal wall, a phenomenon that is not corrected by a possible surgical intervention aimed at the resection of the area of narrowing. It has been observed that survival between patients and patients treated pharmacologically is not very different (5, 6).

The success of a surgical palliative intervention should be aimed at recovering the ability to introduce food for the remaining period. Otherwise it should not be taken into consideration (4). In patients with carcinomatosis, the presence of residual disease, the presence of ascites, the advanced stage, and the presence of multiple levels of obstruction have a negative impact on survival (7). Carcinomatosis caused by colon cancer appears to have a slightly better prognosis than other tumors (8).

Causal treatments

Chemotherapy has never been considered particularly useful in patients with intestinal obstruction, in patients treated with chemotherapy and parenteral nutrition. Treatment was ineffective in resolving the obstruction condition, although patients with ovarian cancer may also have a chance to revert the situation (9). In other circumstances, chemotherapy may have an important causal role, as in the case of large lymph node masses associated with Hodgkin's disease. A surgical evaluation is mandatory in the presence of a diagnosis of intestinal obstruction. Until a few years ago, surgery was traditionally considered an inevitable step. As already mentioned, the scarce general conditions or the extension of disease, the presence of large abdominal masses or the presence of multiple sites of obstruction preclude in reality any heroic intervention. The survival described is between 2 and 11 months (10).

The optimistic surgical evaluations come in general from retrospective series in which there is no selection that can confirm the result (excluding for example the "inoperable", never a well defined category). If anything, the value of an operation for intestinal obstruction can derive from the possibility of a benign cause (11, 12). Benign adhesions or the presence of a single obstructive site can justify a resolution of adhesions or a colostomy.

Adherences are found in 20% of patients and are generally due to chemotherapy. Abdominal detension with the use of the gastric tube may also be useful in these benign circumstances, for example postoperative adhesions, while it is generally not very effective in malignant forms. A patient with metastatic disease is unlikely to have a benign obstruction. The duration of a waiting treatment before taking surgical decisions is not well established. Although surgery allows longer free interval times and a

lower re-obstruction frequency than non-operated, morbidity is very high and survival is not extended (8, 13-16). Many of the operated patients often continue to exhibit obstructive symptoms. Cancer re-obstruction is a predictor of postoperative hospital mortality (17).

The choice of the type of intervention, the primary resection with simultaneous intent of removing the tumor and the obstruction, or treatment of the first obstruction (colostomy) or the resection (staged resection), remains uncertain (18).

The use of self-expanding stents (SEMS) has become a well accepted procedure for colon obstruction and other cases of limited levels of obstruction, both as a temporary (bridge) and definitive form. Postoperative complications are lower and survival seems to be comparable to surgery (19, 20).

Decompressive gastrostomy is an alternative to the long-term use of the nasogastric tube in cases not responsive to medical treatment of gastrointestinal symptoms. In general, life expectancy is not an absolute factor for the surgical decision, unlike the general conditions, the level of suffering, and the symptomatic burden linked to complications and prolonged hospitalization. Postoperative complications include infection, dehiscence, sepsis, fistulae, obstruction, bleeding, pulmonary embolism, and peripheral thrombosis.

Effective surgical palliation should ensure symptom control and intestinal transit for sufficient time to justify intervention. These factors are particularly difficult to evaluate compared to simple parameters, such as mortality and morbidity. The quality of life in this context is difficult to measure.

Parenteral nutrition

The use of parenteral nutrition requires many considerations of a clinical, ethical, moral, and economic nature. There is no data to show that patients with intestinal obstruction treated with parenteral nutrition have a better quality of life and longer survival. An expected 3-month survival is generally considered acceptable in refering a patient to such treatment. It has been reported that the average survival in patients followed at home is about 60 days, of which 1/4 are spent in hospitalizations for the treatment of complications (21). Parenteral nutrition is often considered futile and expensive. While there is no doubt regarding its role in hypophagic patients in which oral feeding is not possible and parenteral nutrition has a substitutive and preventive role for malnutrition, in advanced patients it is unlikely that it will lead to an improvement of some symptoms (fatigue, sense of well-being) in the presence of a state of anorexia and cachexia

(22). This metabolic state does not allow an effective use of nutrients. In these cases the absence of advantages mean a complex and expensive treatment is not justified. A good communication on the inevitability of the clinical condition beyond the symbolic meaning of nutrition allows the right decisions to be made in different clinical contexts (see chapter 2).

Management of gastrointestinal symptoms in inoperable patients

Drug treatment is aimed at reducing the symptoms associated with intestinal obstruction, such as nausea, vomiting, pain, possibly without using the nasogastric tube, a source of considerable discomfort. The parenteral route, intravenous if available, or subcutaneous, is imposed in these circumstances, given the impossibility of using the oral route. In some cases the treatment is also aimed at the recovery of intestinal transit, when the intervention is precocious and the clinical conditions of reversibility exist. In many cases, an association of drugs that act with different mechanisms on gastrointestinal secretions makes it possible to achieve the best results (23).

The most important drugs are based on the ability to reduce gastrointestinal secretions. Anticholinergics have traditionally been used for this purpose, along with analgesics and antiemetics. Substantially, they reduce cholinergic intestinal activity, such as the formation of secretion and muscular tonic activity. Butylbromide scopolamine in doses of 60 mg/day, compared to atropine and scopolamine hydrobromide, seems to be the most tolerated substance due to poor cerebral penetration. Glycopyrrolate is used only in some countries. Corticosteroids can reduce intestinal secretions and wall edema and are therefore used in combination (24). Anti-hystaminic drugs (H1) and hydrogen pump inhibitors have an action predominantly on gastric secretions and therefore they are indispensable for high duodenodjunal obstructions (25), but not very useful in multi-site peritoneal obstructions.

-Butylbromide scopolamine	reduction of cholinergic gastrointestinal secretions
-Corticosteroids	reduction of wall edema, reabsorption of water and salts
-Anti-H2,	exclusive reduction in gastric secretions
- Hydrogen pump inhibitors	
-Octreotide and analogues	reduction of VIP levels and gastrointestinal secretions

Table 2. Mechanisms of antisecretory drugs.

Somatostatin analogs are the most effective drugs, even in comparative studies with other drugs (pump inhibitors, scopolamine, neuroleptics) (1, 10). Octreotide in doses of 0.3-0.6 mg/day has a multifactorial mechanism that enhances its overall activity in many conditions of obstruction: it reduces the secretion of intestinal hormone secretagogues such as the vasointestinal peptide (VIP), decreases the intestinal flow and motility, and reduces the gastrointestinal secretions by promoting the absorption of water and electrolytes. The flexibility of administration (continuous intravenous or subcutaneous administration) is an added value. Its effectiveness has been demonstrated in many studies conducted with different results but substantially able to confirm a notable efficacy (26). A placebo-controlled study has questioned its utility (27). The same study actually shows exactly the opposite when the results are evaluated on the third day from the starting date. The study does not take into account the evidence that the maximal effect of octreotide is obtained only between 2 and 5 days. The study contains other limitations, and lacks a pragmatic approach.

Some studies have been performed with long-acting preparations, demonstrating the efficacy of octeotide (28).

In reality, the multiplier effect of several substances with different mechanisms makes it possible to maximize the result, with recovery of intestinal transit and therefore the ability to cautiously resume oral feeding. The combination of octreotide, corticosteroids, and metoclopramide, facilitated by an induction with an osmotic substance such as amidotrizoate, is perhaps the most robust and intensive treatment (23). The clinical sense in relation to the patient's condition should guide the right combination. For example, in high obstructions, the most resistant to octreotide, in which the overall effect on the other intestinal secretions is lacking, the aid of H1 blockers or hydrogen pump inhibitors could be useful. In inveterate, definitive obstructions, generally in those conditions in which no timely treatment has been effective, metoclopramide should not be administered because of the loss of propulsive effects, and should be replaced with an antidopaminergic antiemetic such as haloperidol, in order to reduce the central sensation of peripheral stimuli coming from the viscera. In table 3, a possible combination sequence according to the severity conditions is reported.

	1st line	2nd line	3rd line
Octreotide	x	x	x (increase the dose)
Corticosteroids	x	x	x
Metoclopramide	x		
Amidotrizoate	x		
Aloperidol		x	x
Ranitidine			x
Hyoscine butylbromide			x

Table 3. 1st line = potentially reversible state (recovery of transit), 2nd line = long-lasting or non-responsive 1-line occlusive state (non-recovery after 5 days), 3rd line = failure to control gastrointestinal symptoms, high obstructions (gastroduodenal).

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CHAPTER TWENTY-TWO E

ASCITES

The appearance of ascites in the cancer patient is relatively frequent (3-6%) and is often associated with ovarian cancer, in which it appears in about 1/3 of patients, and with gastric and biliary tumors. The presence of ascites is synonymous with advanced disease, even if in patients with ovarian cancer higher survival rates may be observable, probably because it is present at the diagnosis and is sensitive to cancer treatment (1).

Symptoms are characterized by the extent of abdominal distension and include abdominal heaviness, dyspnea, anorexia, nausea and vomiting, sense of satiety, esophageal reflux, poor mobilization, insomnia, changes in body image and pain (2).

Pathophysiology

Ascites formation is linked to an imbalance of forces that facilitate or decrease the formation of fluids in the peritoneal cavity. Fluid drainage occurs thanks to the lymphatic system, whereby an alteration due to a compressive tumor, for example, limits the elimination of fluids. On the other hand, the quantity of fluids can be increased for various reasons. An increase in hepatic venous pressure, resulting from liver metastases or large-sized tumors (including benign forms such as Budd-Chiari), produces a fluid passage accompanied by hormonal responses, such as a renin activation, resulting in a retention of water and salts at the renal level, recalling the portal hypertension mechanisms present in degenerative liver diseases (2).

An increased vascular permeability for a peritoneal inflammatory involvement, both for the presence of neoplastic cells and inflammatory substances such as cytokines or angiogenetic factors, leads to an exudation, that is a fluid rich in proteins, which contributes to the formation of ascites through the passage of larger molecules able to exert an oncotic dragging action for liquids. The predominant component of the two mechanisms can be unveiled by the plasma-ascitic gradient of albumin. The gradient correlates to portal pressure and a value >11 g/L is

indicative of the presence of a transudate and the presence of a portal hypertension mechanism. The formation of chylous ascites is mainly observed in retroperitoneal tumors with lesions of the lymphatic structures (3). The diagnosis is based on the clinical examination and the history of the patient. An ultrasound or abdominal imaging exam confirms the clinical picture, also providing therapeutic indications.

Treatment

Guidelines or recommendations for treatment of ascites and related symptoms have been proposed, although it will often be necessary to individualize treatment according to that specific case. Specific antitumor therapy should always be considered, particularly in patients with ovarian or breast cancer, for the possible positive response (4). Peritoneal treatment with chemo-hyperthermia with cytoreductive surgery is often used with good therapeutic responses, although the selection of patients to be subjected to such aggressive treatment remains an unsolved problem (5). Chylous ascites may also be responsive to chemotherapy and radiotherapy. There are numerous chemotherapeutic agents used for peritoneal instillation (3). Other approaches include the use of anti-angiogenic drugs. Octreotide has been proposed for its multiple mechanisms, in tumor forms with an endocrine component.

Diuretic therapy remains the cornerstone of the treatment of ascites in the forms of portal hypertension, although the real efficacy in the malignant forms is more controversial (6). However, patients with a plasma-ascitic gradient of albumin >11 g/L should have the greatest potential for response. Furosemide, and especially spironolactone, are the most used drugs, often in combination. Amiloride is an alternative potassium saver with a shorter action latency.

Paracentesis is another popular modality for the containment of ascites for rapid reduction of ascites volume and the resolution of related symptoms. Fears of hemodynamic complications should be limited in patients in whom there is no elevated albumin gradient. Therefore a few liters can be removed in a couple of hours. The main problem is that reform of ascites is very rapid because, paradoxically, the game of pressures, after the evacuation of fluids and the reduction of abdominal pressure, plays in favor of a rapid passage of fluids into the peritoneum, with the same underlying mechanisms. If the prognosis is short, the indication of paracentesis remains the preferred one. The positioning and the permanence of a peritoneal catheter could be an alternative solution (7), which allows controlled evacuation (with a three-way tap) and can be

continued over time according to needs (8). Adhesive anchoring systems avoid the use of sutures that over a long period produce significant skin lesions. In some cases, the locus of the ascites does not allow complete elimination of the peritoneal fluid. Complications are rare but possible (intestinal perforation, infections). The peritoneo-venous shunt is a somewhat more complex technique that involves a connection with the jugular or femoral vein to discharge the ascitic fluid. There is a certain reluctance towards the technique justified by the frequency of general complications and functioning. The presence of neoplastic cells in the ascitic fluid or a loculated ascite, chylose or hemorrhagic, limit the indications to a shunt.

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CHAPTER TWENTY-TWO F

JAUNDICE

The appearance of jaundice in cancer patients is often an indicator of advanced disease (1). In order to ascertain the causes and to take possibly causal or exclusively symptomatic measures, it is fundamental to understand the mechanisms by which bilirubin is formed and eliminated. The bilirubin produced is released into the circulation (free non-conjugate). Linked to albumin in order to be transported in the plasma it is captured by the liver where it undergoes further modification. The free bilirubin is concentrated in the liver, thanks to the intervention of a series of enzymes, and is conjugated with the glycuronic acid (conjugated bilirubin or diglucuronide or direct). Through the biliary ducts, the conjugated bilirubin arrives in the intestine where it is reduced by the bacterial flora into compounds called stercobilinogens. These substances are eliminated with the feces to which they confer the typical color. A part of bilirubin is instead reabsorbed at the intestinal level and then recirculated to the liver. The portion not reabsorbed by the liver is finally released into the circulation and eliminated with the urine, after being oxidized to urobilin. The increased concentration of bilirubin may have different origins in the cancer patient, especially in relation to the location of the disease.

a) Liver failure

Many tumors have the capacity to produce liver metastases, especially gastrointestinal tumors. Jaundice is a common complication of impaired liver function. An intrahepatic cholestasis is linked to a cellular lesion and minor ducts, typically not associated with dilatation of the major biliary tract and therefore not to be treated with mechanical interventions. In cancer patients a massive structural invasion is observed, accompanied by other signs of liver failure. In these cases, jaundice is the sign of a very poor prognosis. Patients therefore exhibit the typical signs of hepatic insufficiency, with hypoalbuminemia, coagulation abnormalities, and cognitive abnormalities, linked to metabolic disorders, in particular an

imbalance in the distribution of amino acids, promoting the passage through the blood-brain barrier. If chemotherapy can also provide some responses, caution is required for increased toxicity and therefore a very bad therapeutic response. An intrahepatic cholestasis is also observable after bone marrow transplantation as an expression of a graft-versus-host disease.

b) Biliary obstruction

Tumors can instead cause an obstruction of the main biliary tract. Proximal obstruction is often linked to cholangiocarcinoma, intrabiliary metastasis, or a lymph node mass. The obstruction of the common duct is frequently to be attributed to pancreatic cancer. Even a thrombosis of the bile duct can produce jaundice.

From a clinical point of view, patients with jaundice are defiled, weak, with fatigue, nausea, anorexia, pruritus, and septic phenomena linked to cholangitis. The presence of clear stools suggests a cholestasis due to the lack of bilirubin staining. The liver may be of increased volume and neuropsychiatric symptoms are often associated with somnolence and confusion. Bilirubin values will be increased. The increase in free or indirect bilirubin is found in pre-hepatic forms, for example after hemolysis, where the ability of the liver to metabolize is exceeded. The reduced bilirubin uptake by the hepatocyte, the reduced conjugation with the glycuronic acid, or the reduced excretion with the bile, due to hepatic pathologies, instead determine a conjugated hyperbilirubinaemia (hepatocellular jaundice). If direct (conjugated) bilirubin is higher than unconjugated (indirect), the hepatocyte is not able to eliminate bilirubin (hepatitis, drug reactions), or a downstream obstruction exists. Liver enzymes are often observed for direct or retrograde cellular distress. Increases in gamma-glutamyl transferase (especially in drug lesions) or alanin-aminotransferase are observed in cholestasis. There are numerous instrumental investigations that can clarify the anatomical features of the biliary tract and formulate a diagnosis of location and mechanism. Imaging studies, ultrasounds, retrograde endoscopy of the biliary tract, or cholangiography are more sophisticated means, some of which are interventional for both an adequate visualization and to carry out a consequent treatment.

Treatment

Chemotherapy may be used in patients with chemo-sensitive tumors even in the presence of jaundice and biliary tract involvement, possibly supported by biliary drainage, as well as a jaundice sustained by a biliary tract infection possibly responding to appropriate treatment (1). Biliary drainage procedures allow for clinical recovery in patients judged to be inoperable. Biliary stents introduced by endoscopy produce a success similar to the surgical ones but are associated with less morbidity and complications (2), considering that the average survival is limited. Often jaundice is associated with a series of very disturbing symptoms, such as itching, anorexia, and fatigue. When the general conditions and prognosis allow it, biliary stents are as effective as surgery – with obvious minor complications – especially those of the latest generation which are able to prevent and reduce intracavitary growth as well as being removable. These advantages must be counterbalanced with the possibility of migration. The most common complications are infections and obstruction.

In more advanced patients with shorter perspective, the treatment may be symptomatic only, particularly in the forms of intrahepatic jaundice, where there are no prosthetic or surgical indications. Itching seems to be due to irritation of skin receptors by bile acid and other toxic substances subject to enterohepatic circulation. Substances capable of removing these pruritogen agents possess the ability to impact on the symptom. While antihistamines do not seem to offer particular benefits, ion exchange resins bind bile acids and promote fecal excretion of these substances by removing them from reabsorption and enterohepatic circulation. Cholestyramine in doses of 16 mg per day is the most widely used substance. The most significant problem is constipation and flatulence. Rifampicin is a pregnane X receptor agonist that induces the production of oxidative enzymes that influence the secretion of toxic substances that induce itching. It also competes with the reabsorption of bile acids. The doses are 300-600 mg/day. Opioid antagonists have been proposed serendipitously with the observation in some patients with the appearance of pruritus after opioid administration and improvement after use of naloxone. Efficacy has been confirmed in controlled studies. The recommended naltrexone doses are 50 mg/day (3). Considering these possible relationships with the opiodergic system and in turn with that of serotoninergic and gabaergic systems, consequently some other drugs have been used occasionally successfully, such as phenobarbital, haloperidol, setronics, or propofol. Other benefits may be non-pharmacological, such as the use of emollients or light clothing (4).

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CHAPTER TWENTY-THREE

SYSTEMIC SYNDROMES AND SPECIFIC CONDITIONS

CHAPTER TWENTY-THREE A

CACHEXIA-ANOREXIA

Cachexia-anorexia syndrome is a multifactorial form characterized by weight loss, and is typical of advanced disease. It is associated with a decrease in physical abilities, treatment tolerance, and survival. Patients with reduced muscle mass due to catabolic state are refractory to cancer treatment. The consequences are devastating for the psycho-physical function, body image, and quality of life (1). The prevalence is quite variable according to the definitions and criteria adopted. Many tumors, such as those of the stomach and pancreas, have a high incidence, although the patient's genotype or tumor phenotype may influence the prevalence of the syndrome in individuals.

It is characterized by complex interactions leading to higher energy expenditure, inhibition of protein synthesis and proteolysis, lipolysis, and an alteration of the mechanisms regulating appetite (2). Contrary to what is observed with fasting, which in some ways has major metabolic alterations but also an attitude to saving, weight loss cannot be compensated with nutritional support (3) (table 1).

	Cachexia	Fasting
Caloric intake	-	---
Energy expenditure	- +	-
Lean mass	-	--
Body fat	-	--
Insulin	+	-

Table 1. Differences between fasting and cachexia

Often there is no timely diagnosis due to the uncertainties about the definition. Cachexia has been defined as a multifactorial syndrome characterized by a loss of muscle mass (with or without fat mass) that is not reversible by conventional treatments and that leads to a progressive clinical deterioration. The diagnosis is based on the presence of one of the elements shown in table 2.

- weight loss of >5% in the previous 6 months - body mass index <20 and a weight loss of >2% - presence of sarcopenia (<7-26 kg/m2 in males, <5.45 kg/m2 in women) and a weight loss of >2 kg.

Table 2. Diagnosis of cachexia

Cachexia presents in a continuous and progressive form generally divided into three phases: pre-acute, cachexia, and refractory cachexia, although a patient will not necessarily pass through all three phases. In the first phase, some clinical signs, such as anorexia and a reduced tolerance to carbohydrates, can precede weight loss (≤5%). The subsequent progression will depend on numerous factors, such as the type of disease, the pre-existing state of inflammation, the low caloric regimen, and the lack of therapeutic response. Patients with any of the previously reported diagnostic features are considered to be affected by overt cachexia, which becomes refractory due to disease progression. In this phase catabolism prevails and a series of factors prevent the maintenance of body weight, associated with a deterioration of the performance status and a survival of less than 3 months.

The severity depends on the weight variation and depletion of lean and fat mass. A loss of 5 kg/m² of body mass index has more important implications in patients who start from pre-existing values already below the norm.

The primary causes of cachexia are dependent on the direct effects of the disease or the inflammatory response, while the secondary causes are represented by further factors that decrease the appetite or increase the losses of lean and fat mass, such as nutritional disorders associated with symptoms such as constipation, nausea, depression, pain, sense of satiety, changes in taste, or associated metabolic alterations.

Pathophysiology

The pathophysiology is characterized by a negative protein and energy balance due to the combination of a reduction of food intake and an abnormal metabolism. The propulsive mechanisms of the syndrome are multifactorial and interdependent. They include the inflammatory reaction, endocrine alterations and those of the sympathetic system, those factors that limit food intake, and specific factors of the tumor. However, the inflammatory reaction must be considered the fundamental pivot of these processes.

Cytokines are low molecular weight proteins, produced by lymphocytes and macrophages, which function as intercellular messengers at the level of various tissues in the periphery and centrally. At the peripheral level, the proinflammatory cytokines, interleukin 6, the tissue necrosis factor, and inteferon act on the muscle genetic modulation, inhibiting the transcription of muscle protein synthesis (myosin, actin, troponin, tropomyosin) or modifying its balance, and activate the synthesis enzymes that regulate protein degradation. In addition, positive modulators for protein synthesis, such as growth hormone, are downregulated. Loss of muscle proteins may depend on cytokine-induced activations of lipase in fat tissue and a consequent increased expression of proteosomal enzymes. The cytokines also induce insulin resistance, oxidation products, and increased energy consumption (4).

At the level of the central nervous system, systemic cytokines exert a powerful effect, increasing the expression of hypothalamic cytokines and inducing the synthesis of a further messenger, such as nitric oxide or prostanoids, and stimulating some nerve pathways. At the hypothalamic level the sense of appetite is mutually regulated by leptin in adipocytes, with an anorexic power, and by ghrelin in the stomach, with an orexizing action. The cytokines mimic the signals of the anorectic action of leptin, while inhibiting the stimuli of ghrelin and Agouti peptide. They also activate the anorectic pathways at the level of the arched nucleus with the release of the hormone that stimulates the melanocytes. This substance inhibits the appetite and increases energy expenditure by activating the melanocortin receptors. The peptide called Agouti is an antagonist of such receptors. It is expressed physiologically in the jejunum and stomach by hypothalamic ghrelin and is inhibited by leptin. The central activation of the hypophysis–hypothalamic–adrenal axis is probably the true central connection with the release of interleukin 1B. Endogenous corticosteroids, through ACTH activation, probably act in tandem to produce muscle atrophy.

Despite these important pathogenic mechanisms, the relationship between cytokines and clinical aspects does not always seem so evident. Many studies have found that high levels of interleukins correspond to weight loss, worsening of general conditions, and limited survival, while others have shown the opposite (5). The formation of local cytokines may have a prominent role in some phases of the disease, such that systemic concentrations do not reflect the activity of tissue cytokines. Furthermore, the tumor phenotype, the stage of the disease, the dosage methodology, or a genetic variation in the immunological response can strongly influence

the relationship between the plasma concentrations of cytokines and clinical events (6).

C-reactive protein is a prognostic marker useful for some cancers, and similar in meaning to IL-6. Other than being a marker it may also have a role in the development of the inflammatory reaction. NK-kB regulates the transcription and expression of many factors involved in inflammation, such as nitric oxide, COX-2, and other cytokines. It appears to be the intermediary of TNF-α in the inhibition of muscle synthesis and in the stimulation of factors that induce degradation.

Muscle atrophy is caused by a decrease in protein synthesis and a concomitant increase in degradation. In addition to the action of cytokines on synthesis systems, some proteolytic reactions at the liposomal level are activated locally. Positive regulatory factors such as insulin-like growth factor are downregulated, while negative factors such as myostatin are overexpressed.

The reduction of body fat takes place very quickly. It is determined by several factors, such as the reduction of food intake, tumor factors, and inflammatory agents that inhibit lipogenesis and promote lipolysis.

The syndrome is also characterized by a reduction or a greater resistance to metabolic hormones. The ghrelin produced by gastric cells increases appetite and gastric mobility. It is the only hormone that is orexizing and its plasma concentration is inversely proportional to the body mass index. The ghrelin also seems to have effects on the muscle independently of the growth hormone. In cachexia, a compensatory increase in ghrelin is observed, such as in fasting or anorexia nervosa, but an increased resistance to its effects is observed in the tissues. Androgen hormones have direct and indirect anabolic effects in the muscles. Testosterone increases muscle mass thanks to an increased myosin synthesis and opposes the effects of corticosteroids. Reduced testosterone levels influence the prognosis and are associated with loss of appetite, decreased quality of life, and asthenia. Some drugs, including corticosteroids, opioids, and megestrol, reduce testosterone levels and consequently promote hypogonadism.

Insulin reduces appetite by acting hypothalamically. At the peripheral level, however, it has anabolic effects on muscle and fat tissue. Cachexia is associated with increased insulin resistance, which at the muscle level increases synthesis and decreases protein degradation.

The increase in energy expenditure observed in cachexia is the result of the induction of a futile metabolism, such as the activation of the Cori circle in which the lactate produced by the tumor is converted to glucose

in the liver, which is an inefficient system to produce ATP, or an increased expression of mitochondrial proteins leading to greater thermogenesis.

The formation of an excess of superoxides, due to tissue toxicity, is normally overcome by antioxidant protection systems, such as glutathione, melatonin, and other enzymes. The superoxides, activated by numerous mechanisms of cachexia, are activators of NF-kB, which in turn induces a proteolytic cascade at the muscular level.

Finally, in cachexia there is a dysregulation of the vegetative system, typical of the advanced stage of the disease, with gastrointestinal and cardiovascular symptoms, known as vegetative dysautonomia due to a polyneuropathy (7). An important part of the syndrome is to be attributed to the decrease in food intake, as a consequence of the symptoms associated with the evolution of the tumor, such as early satiety, decreased intestinal transit, pain, changes in taste, constipation, and depression.

Assessment

A 5-10% reduction in body weight seems to be a well-accepted criterion for a diagnosis of malnutrition resulting from a cachexia-anorexia syndrome and remains a simple and well validated measure. Some key points will need to be explored properly:

a) Anorexia or decrease in food intake. The amount of foods introduced, particularly proteins, is a fundamental starting point. Central causes that reduce appetite, sensory alterations (dysgeusia, dysosmia), alterations of the gastrointestinal tract (nausea, early satiety, constipation) must be sought. Secondary causes, such as stomatitis, pain, dyspnea, and inconvenient eating habits, for example, are reversible causes.

b) Hypercatabolism produced by the tumor itself or by systemic or mediated inflammation is a relevant component of cachexia. C-reactive protein is the most accepted index of inflammation, although cachexia is not always attributed to inflammation. Therefore, other indexes to consider are the response to treatment and the progression of the disease, both of which may be indirect indexes of catabolism. Other factors, such as resistance to insulin, prolonged treatment with steroids, hypogonadism, and an increase in energy expenditure, have to be considered.

c) The study of muscle mass and strength. There are several imaging studies that can evaluate muscle size, together with the analysis of muscle bio-impedance, useful for patients without major changes in body composition. Dynamometry is used to evaluate muscle strength.

d) Functional and psychosocial effects. The most used tools are the EORTC Quality of Life Questionnaire [QLQ] -C30, the ECOG see chapter 5), and the Karnofsky status, together with a series of questions useful to understand how a reduction of food intake affects one's own functional status.

Treatment

Weight loss is associated with a worse prognosis and survival in cancer patients. Since the syndrome is in some way linked to the evolution of the disease, and in fact is reversed by clinical response to the disease (8), its specific treatment has never found an adequate clinical response. Treatment should be based on pre-existing conditions with respect to the disease and the mechanisms that are more likely to contribute to weight loss and possible reversibility (see figure 1). The treatment is aimed at reducing anorexia, attenuating systemic inflammation and muscle catabolism, by stimulating the protein metabolism. Therefore a multimodal approach is foreseen that must necessarily be performed early, as opposed to at the advanced stage of the disease where it is impossible to reverse the syndrome or prevent a further decline.

Currently there is no specific strategy. Theoretically, a caloric supplement could be the most logical solution, but the benefit seems to be quite limited to patients who have not actually developed the syndrome, as in postoperative period, in irradiated patients or those undergoing bone marrow transplants, or in patients who have diseases potentially reversible or which present a clinical response. Very heterogeneous studies have shown that enteral or parenteral support does not lead to advantages in advanced cancer patients (9). Although nutritional support allowed weight gain, it did not increase survival. In particular, parenteral nutrition is not considered a standard of care, although a limited number of patients can benefit from it. However, it was never possible to identify predictive factors to refer to (10). On the contrary, in the presence of poor appetite, often the contention between family members and patients around the necessity of force feeding results in an asphyxiating condition from the psychological point of view.

When a decision is made to initiate a pharmacological treatment for anorexia-cachexia, progestinics and corticosteroids are the most common drugs used to improve appetite. Many studies have suggested that progestinics, such as megestrol and medroxyprogesterone, increase appetite and body weight in advanced patients with anorexia (2). Suggested doses are 160 mg up to 800 mg/day of megestrol. Although these drugs are generally well tolerated, possible complications include thromboembolic risk, edema, hyperglycaemia, and adrenal and adrenergic suppression, as well as increased mortality (11). Corticosteroids exert their effect thanks to the anti-inflammatory action and probably a direct effect on the hypothalamic centers. Their effectiveness on appetite is supported by some controlled studies. The numerous side effects are reported in chapter 12. No difference in efficacy was observed between progestinics and corticosteroids (12). Therefore corticosteroids should be reserved for patients at thromboembolic risk or patients with limited survival (4).

Muscle exercise may be important for the maintaining of muscle function through the modulation of muscle metabolism and increased sensitivity to insulin, even if large levels of evidence do not exist (13). Other drugs have been proposed, without clinical successes being achieved. They include dronabinol, cyproheptadine, pentoxifyline, and eicosapentaenoic acid. Treatments exist, however, promising enough that they await an appropriate clinical evaluation. Melatonin reduced TNF-α levels and showed an effect on clinical response, weight, and survival in lung cancer patients receiving chemotherapy. Thalidomide produces similar effects and has shown a positive effect on the sense of well-being of very advanced patients (14). Ghrelin signals the availability of nutrients from the gastrointestinal tract to the central nervous system, stimulates appetite, and reduces energy expenditure through a series of hypothalamic mediators that act both centrally and peripherally, induces neuro-endocrine and inflammatory signals to increase muscle growth, decreases protein catabolism, and increases lipolysis, reducing the use of fats. It therefore acts as an energetic sentinel of the human body, probably with other extrahypothalamic actions in its hedonistic aspects, of mood and anxiety, sleep regulation, learning and memory, and neurogenesis (15). Recently, it has been reported that anamorelin, an analog of ghrelin, determines after 3 months an increase in lean mass, compared to placebo (16).

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CHAPTER TWENTY-THREE B

FATIGUE

Fatigue is one of the most frequent and devastating symptoms in patients with advanced disease, able to interfere with quality of life and with physical and social activity. Fatigue is a consequence of both the disease and the treatment. It can precede the diagnosis or present itself after the first courses of therapy and remain long after the end of a treatment (1).

Pathophysiology

The mechanism still remains unclear. Although predominant, it is often associated with a corollary typical of other symptoms that contribute to the genesis and severity of fatigue. Often, many of the causal factors are concomitantly present and self-sustaining. Cancer is able to produce a series of inflammatory substances, such as cytokines, tumor-necrosis factor-α (TNF-α), and interleukin (IL), active on both muscle and central nervous tissues. Malnutrition, loss of lean mass, and progressive cachexia are invariably associated with fatigue and are phenomena closely related in a very complex way. With the same weight loss, cancer patients have higher energy consumption with a protein catabolic attitude compared to controls. On the other hand, some commonly used drugs, such as corticosteroids, produce mitochondrial alterations that lead to a myopathy (2). Prolonged rest leads to a loss of muscle mass, with a loss of endurance and daily physical activity. In fact, exercise has a beneficial effect on muscle function (3). However, disproportionate efforts, especially in young subjects undergoing treatment, in an attempt to maintain a social and professional standard, can result in fatigue.

At the central level, a role of the reticular system on fatigue has been hypothesized. This system receives many sources of information. Chronic stimuli, such as pain, for example, can generate fatigue through this regulatory system and its influence on descending activities. Cerebral masses can be a cause of fatigue, as well as cognitive disorders in a mutual way. The same inflammatory substances produced by the tumor can induce “mental” fatigue. The dysfunction of muscle activity, typical of cachexia,

can be another cause of fatigue, even if it can also appear in the absence of malnutrition and the maintenance of body weight. In the muscle there is an increased lactate formation and an alteration of various enzymes that alter muscle biochemistry, which results in a decrease in muscle strength at rest and under stress. On the other hand, weight loss from malnutrition is observed in some cases, without fatigue (for example in anorexia nervosa). Moreover, in particular hypercatabolic forms (sepsis, post-operative period), anorexia and fatigue are a consequence rather than the cause of metabolic abnormalities. Infections, which often appear in defedated patients undergoing treatment, are known to produce muscle weakness due to metabolic changes in the muscles in the catabolic direction.

Inflammatory substances produced by tumor
Muscle abnormalities
Muscle deconditioning
Alterations of the central system
Insomnia
Chronic hypoxia
Cachexia
Infections
Anemia
Dysautonomia
Psychological aspects
Endocrine abnormalities
Paraneoplastic syndromes
Side effects from cancer treatment and drugs

Table 1. Causes of fatigue

Anemia is frequently observed in cancer patients. Bone marrow depression, food deficiencies, hemolysis, malnutrition, and chronic bleeding are associated with fatigue when hemoglobin values are reduced (<8 g/dl). Dysautonomia is a frequent finding in advanced disease. This syndrome is characterized by postural hypotension, malnutrition, nausea, anorexia, and fatigue (4). Anxiety, depression, and in general psychological distress, are often associated with fatigue, even if the interrelation between these components is complex and mutual. Insomnia and chronic hypoxia are invariably associated with fatigue. Metabolic and electrolytic alterations are possible causes of fatigue. Testosterone deficiency is associated with muscle loss, fatigue, reduced libido, and anemia. On the other hand, the oncological treatments or the use of opioids

can cause hypogonadism. Alterations of the hypothalamic–pituitary–adrenal axis of various origins, especially induced by a generalized inflammatory state, can be further contributing causes to fatigue. Paraneoplastic neurological forms, by deteriorating neuromuscular transmission, can generate fatigue. The appearance of fatigue is commonly observed after chemotherapy or radiotherapy by mechanisms that are still unknown. Finally, many drugs, such as opioids and, in general, agents on the central nervous system, and diuretics can produce fatigue (1).

Assessment

Fatigue is a subjective and multidimensional sensation, therefore difficult to quantify. The beginning, the duration, and the interference with daily activities and its psychological consequences will have to be verified. Karnofsky and ECOG are the simplest tools used to evaluate the level of physical function. Beyond the numerical scales (ESAS items), some instruments are more specific (Functional Assessment of Cancer Therapy – Fatigue (FACT-F) or the Brief Fatigue Inventory (BFI). The FACT-G presents multidimensional scales that evaluate the intensity of fatigue and quality of life. The BFI measures the severity and effects of fatigue on daily activities over the previous 24 hours. A tool particularly used in research is the EORTC QLQ-C30, although in advanced patients it presents a ceiling effect. Finally, there are multidimensional tools that offer the most relevant aspects. The assessment of fatigue in reality should not be performed without a broader vision that includes all the factors involved in the analysis. For an initial screening and then a specific attention to the problem, patients could be categorized according to cut-offs very similar to those used for pain (0-3 mild, 4-6 moderate, 7-10 severe) (1, 2).

Treatment

Given the large concausality of fatigue, the identification of the main factor which can be reversed should be a priority. It will therefore be necessary to establish how much fatigue is relevant to the patient, which main cause underlies this symptom, and whether there are measures to reverse the identified cause, even if in some cases it will not be possible to have certainty of the cause. In many cases, especially at an advanced stage, the most realistic goal is to reduce the feeling of fatigue rather than eliminate it altogether. Information is essential to provide realistic expectations and to achieve better physical and mental cooperation from patients. As the disease progresses, the patient must be able to readjust to

physical limitations by measuring the energy and activities possible. Deconditioning should be used, perhaps with the help of a physiotherapist who suggests the most suitable exercises (5). Patients with fatigue can benefit from exercise and there is no evidence that this could worsen the clinical picture. In fact, physical exercise improves sleep, physical function, and sense of well-being (6). Occupational therapy can help, especially at home to provide physical help for necessary activities.

In patients with fatigue without the recognition of a specific treatable cause, numerous pharmacological treatments have been proposed (7). In several studies, corticosteroids have shown a good efficacy in the control of fatigue. At the same time they can also reduce other associated symptoms such as nausea, poor appetite, and pain (8). It is assumed that the mechanism is linked to the anti-inflammatory action against the cytokines. However, the effect is temporary and not prolonged over time. Megestrol acetate has shown a rapid improvement in fatigue and well-being in some studies. The effect should be charged to the corticosteroid and anabolic action. This data has not been confirmed by a re-analysis of existing data, which instead emphasizes the risk of thromboembolic, metabolic, and hypertensive effects (7).

-Causal treatment
Cachexia
Anemia
Infections
Endocrine abnormalities
Psychological alterations
Hypoxia
Pain
Deconditioning
-Non-pharmacological treatment
Information
Physical therapy
Occupational therapy
-Pharmacological treatment
Corticosteroids
Psychostimulants

Table 2. Fatigue treatment

Reduced levels of plasma testosterone concentration, resulting from chemotherapeutic or hormonal treatments, are often seen in advanced patients. Replacement therapy has been used primarily in patients with hypogonadism (9). Methylphenidate inhibits the re-uptake of noradrenaline and dopamine, increasing its presence at the synaptic level. With dosages of 15 mg/day, the data seem controversial, also depending on the differences in population and stage of disease reported. It can produce an indirect effect in patients with opioid-induced somnolence. Modafinil has demonstrated a certain effectiveness in reducing fatigue in patients undergoing chemotherapy (10). In recent years various other treatments have been proposed (mazindol, donepezil, L-carnitine, ginseng), which have not given particular results. From the point of view of scientific evidence, there is no special treatment of particular choice for the treatment of fatigue in advanced patients. The most conclusive data indicate modafinil and methylphenidate, while desametazone, anti-inflammatories, armodafinil, amadanthine, and carnitidine did not provide linear evidence of their efficacy (11).

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CHAPTER TWENTY-THREE C

ORAL CAVITY

The mouth has a prominent role in many aspects of daily life, including vital activities, such as nutrition and hydration, and social and relational activities by phonation and other functions. Alterations of the oral cavity, beyond the associated symptoms, limit the nutritional capacities and therefore can modify in some way the survival or the response to treatment. In the advanced stages of disease there are numerous conditions in which the oral cavity undergoes important alterations that may influence the various functions.

In recent studies of advanced cancer patients, the main symptoms of the oral cavity, mucositis, xerostomia, and dysphagia, were strongly correlated (1, 2). The prevalence of mucositis in advanced patients was 22.3%, with a reduction in the ability to ingest foods associated with low Karnofsky and head-neck tumors. Xerostomia was present in 40% of patients and was associated with the use of many drugs, such as opioids (78%), corticosteroids (75.3%), and diuretics (70.2%). The prevalence of dysphagia was 15.4%. Dysphagia for liquids was present in 52.4% of patients with a major restriction on food ingestion. In 53% of patients it was necessary to use alternatives to the oral route for the administration of drugs. Dysphagia was associated with a low Karnofsky and head-neck tumors (1). Therefore the worsening of general conditions with the progress of the disease, particularly in head-neck tumors, requires special attention be given to the increased risk of oral problems. Unfortunately, the problem is strongly underestimated. For example, 78% of patients had not received information on oral problems (2).

Mucositis

Chemotherapy treatments with paclitaxel, doxorubicin, and etoposide, and local radiotherapy for head and neck tumors, frequently cause damage to the oral mucosa and esophageal interferences with the mechanisms of cell mitosis and regenerative capacities. Poor nutritional status and overlapping infections promote an aggravation of mucositis that generally

appears within a week of treatment to persist for a few weeks in cases without complications. Mucositis is characterized by local pain-burning, especially during the passage of solids and liquids (3). Therefore it can interfere greatly with feeding and reduce the sensation of taste.

Infections

Infections frequently affect the oral cavity. The most common infections are fungal, especially candida. Especially debilitated patients with immune impairment, chronic illnesses, poor oral hygiene, or receiving drugs such as corticosteroids, antibiotics, or cytotoxic therapies are at particular risk of developing oral mucosa infections. The pseudomembranous form is the most common and is characterized by a whitish patina of the mucous membranes and of the tongue, rather resistant to mechanical removal. In other cases, acute forms are observed with an atrophic-flat appearance associated with a burning sensation, for example from superinfection after antibiotic treatment. The diagnosis is visual but can be confirmed by a local levy for a laboratory test. The most common viral infection is represented by herpes simplex. This infection is often reactivated by immunosuppression phases such as radiotherapy and chemotherapy treatments. It is characterized by typical vesicles in the pharyngeal, oral, and labial cavity, with a tendency to multiplication and ulceration. It is accompanied by pain and dysphagia.

Xerostomia

Xerostomia is a state of dry mouth. It is a very common symptom, little considered, and is associated with many clinical conditions. For example, a disease itself, as in head and neck tumors or compressions on the salivary glands, can cause xerostomia. Radiotherapy, surgical treatments, and, especially, the use of drugs such as anticholinergics, antihistamines, diuretics, opioids, anti-inflammatories, corticosteroids, and H-pump inhibitors reduce the formation of salivary secretions with different mechanisms. Often the state of dehydration, due to a lack of intake of liquids with the diet, or increased losses (diarrhea, vomiting, haemorrhage, fever, oxygen therapy) produces this sensation. In the advanced stages it was observed that a load of anticholinergic drugs is progressively important in the determinism of dry mouth (4). From a clinical point of view the main consequences are the loss of protection of saliva against infectious agents, difficulty in chewing and swallowing, as

well as a burning sensation and dryness with loss of appetite, which have obvious consequent effects on nutritional status.

Osteonecrosis of the jaw

A serious complication of the oral cavity regards osteonecrosis of the jaw, associated with the prolonged use of bisphosphonates, and more recently to inhibitors of RANKL, such as denosumab (5). It is more likely that there are local pre-existing favorable conditions, such as poor local hygiene with local pH alterations, that favor the action of these substances that reduce bone resorption (6). Other factors may increase the risk, such as diabetes, the use of corticosteroids, and the state of immunosuppression. Clinically, it presents itself as a painful swelling of the jaw which tends to necrotize itself with the formation of internal and external fistulae.

Treatment

Treatments for mucositis have shown limited efficacy. Aminophosphine, benzydamine, honey, or local anesthetic substances have been used with some good benefit. Morphine in a 2/1000 solution demonstrated some local efficacy, independently of the systemic effect (7). Zinc sulfate and cannabinoids have been proposed for dysgeusia. Antifungals are the specific treatment for mucositis due to a candida infection. Nystatin is available in many forms including oral suspension, to be administered every 6 hours (5 ml). The treatment should be maintained for a few weeks. Fluconazole is the most effective drug and can also be given intravenously (100-200 mg/day), whereas itraconazole appears to have a wider spectrum. These drugs possess an important potential for interaction with other substances that are substrates of CYP3A4 (see chapter 14). Some fungal agents may show a particular resistance that can be overcome with a new generation of antifungals, such as posaconazole. The side effects are predominantly gastrointestinal, nausea and diarrhea, whose severity in some cases requires the discontinuation of antimycotics. For herpetic mucositis, acyclovir is available in various formulations. Penciclovir has been more recently introduced in the form of local cream.

The primary treatment of dry mouth involves the recognition of the main cause and the removal or correction in cases where possible. In some cases, a dental evaluation can exclude or correct local factors. Symptomatic therapy consists of salivary substitutes. Pilocarpine is a cholinergic-muscarinic drug quite effective in increasing the residual

secretion of the relevant glands, even in the most destructive forms caused by radiotherapy (8). The doses are 15-20 mg/day. Pilocarpine is more efficient and above all more durable than artificial saliva, which has an ephemeral effect (9). There are many varieties of salivary substitutes available, based on cellulose, associated or not with antimicrobial agents. However, pilocarpine has consequent side effects of a cholinergic type, with sweating, tearing, and abdominal cramps, and it becomes contraindicated in glaucoma. Alternatively, chewing gum with a mechanical and chemical action, can stimulate saliva production (10). Some cytoprotective agents, such as amifosphine (150 mg) can be used in advance (e.g., of radiotherapy) with reasonable margins of success (11).

The treatment of mandibular osteonecrosis is related to the stage of the disease and the extent of the lesion. Conservative therapy involves the use of antibiotics and local or systemic antibiotic solutions. Surgical revision is indicated in patients with non-responsive disease. Alternatively, the use of teriparatide, derived from the parathyroid hormone, is suggested for the healing of the bone lesion. Experimental therapies include the transplantation of stem cells, hyperbaric oxygen, bone grafting, the application of platelet growth factor, and local laser therapy. Antibiotics can improve local conditions in the presence of frequent superinfections. In reality the only effective treatment is prevention, which involves a dental evaluation and an absolute control of the buccal hygienic state before starting a treatment at risk of mandibular lesion and a frequent revision to treat caries and local infections (12).

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CHAPTER TWENTY-THREE D

DYSPHAGIA

Dysphagia is one of the most relevant symptoms of the oral-pharyngeal tract. Dysphagia is a dysfunction, consisting of difficulty in swallowing, with an alteration of the correct transit of the bolus in the upper digestive tract. It can concern solid foods alone, or even semi-liquid or liquid foods. Dysphagia that progresses over a few months indicates the presence of a tumor. It is often associated with pain and airway passage of foods with a temporal evolution ranging from coughing and spasms to pneumonia. It is the initial symptom of esophageal cancer or the expression of a thyroid or mediastinal tumor. In addition to being dependent on the presence of the primary esophageal disease, it may result from a secondary location, or a surgical treatment, radiotherapy or chemotherapy. Paralysis of the recurrent nerve or impairment of the low cranial nerves can compromise the neurological function of the pharynx, which requires the intervention of numerous muscles for a complex and coordinated action. Many neurological diseases, such as cerebral vascular diseases, tumors, or advanced Parkinson's disease, are characterized by dysphagia (1). Mucositis, infections, and xerostomia are other important reasons for the appearance of dysphagia. Finally, dysphagia may be an expression of intense asthenia and muscle fatigue, phenomena associated with limited survival, whose appearance is considered prognostically poor (2).

Dysphagia for solids suggests a mechanical obstruction, whereas dysphagia for liquids and solids, as well as intermittent symptoms, suggests a neuromuscular disease. From the clinical point of view, difficulty in controlling the bolus in the oral cavity with loss of saliva or food from the mouth, cough, feeling of suffocation by aspiration in the airways, and nasal regurgitation, but also fatigue during the meal, multiple swallowing for the same bolus, and intake of certain postures during swallowing, prevail. Esophageal dysphagia, on the other hand, can occur with a sensation of food stuck in the lower part of the throat or in the thorax, pyrosis, or odynophagia. Physical examination is not always conclusive if not for the presence of local masses capable of compressive tumors on the esophagus. Endoscopy allows the diagnosis of a tumor, or

the highlighting of a tumor or fibrotic shrinkage, and possible infections, as well as highlighting abnormalities in muscle motility, better specified with manometry. The eaten meal allows us to observe the passage and the deformations of the esophagus.

Treatment

The treatment of dysphagia depends on the cause. Depending on the severity and cause of dysphagia, some approaches may work better or worse. The communication of these aspects to the patient is essential to explain the symptoms of the disease and the possibilities of treatment, in particular some dietary measures.

The nutrients and methods of administration must be tested to cover the right caloric load, pending a resolution of the cause. Suggestions include the use of soft foods such as yogurt, pudding, ice cream, and jellies. It could be possible to liquefy other solid foods with added milk, sauces, or butter, and to accompany swallowing with sips of water. Meals should be restricted but repeated at short intervals. In the case of weight loss, energy supplements could increase the caloric quota. Dry foods that are difficult to swallow should be avoided. In the presence of pain, common analgesics will be used. Particular attention should be given to the oral cavity, mucositis, infections, xerostomia (see previous steps). In some cases, such as in neurological forms, certain maneuvers, such as turning the head sideways, can prevent pulmonary aspiration of food. In the forms in which a spasticity condition of the esophageal muscles prevails, various drugs have been suggested, such as Ca ++ - antagonists, nitroglycerin, and anticholinergics, especially in cases where an excess of undigested saliva is formed. Corticosteroids may offer relief in infiltrating forms with an edemigenic component, particularly in eosinophilic esophagitis. In the presence of an obstacle to swallowing, obstruction must be removed.

Self-expanding stents were a fairly effective weapon compared to other intervention modalities. Some anti-reflux stents may result in better results and less complications. High doses of brachytherapy may be a fairly effective alternative treatment. The stent-brachytherapy combination prevents the need for reoperations. The insertion of rigid plastic tubes, dilatation, or chemotherapy is less effective for palliation of dysphagia, due to the high incidence of late complications and the reappearance of dysphagia (3).

If swallowing is not possible, alternative forms of enteral nutrition should be used. This option may be temporary, to allow acute nutrition in

an attempt to remove the main cause, if possible, or may be a definitive solution, if dysphagia could not be treated otherwise. The nasogastric tube is generally unwelcome in the long term for the aesthetic sense, the loss of sense of flavors, the discomfort, and the increase of salivation, so for prolonged treatments gastrostomy should be the choice. In the advanced phase and in the last days of life this indication decays because dysphagia is an expression of an overall general decay and a short-term prognostic factor, in which nutrition loses its value (see chapter on bioethics and communication).

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CHAPTER TWENTY-THREE E

NUTRITIONAL ASPECTS

Malnutrition is prevalent in cancer patients (40-80%). Malnutrition is caused by numerous factors related to the disease and treatment, and has psychological repercussions. In particular, some tumors, such as the head-neck or gastrointestinal varieties, are more risky. Many studies have shown that the prognosis of patients with malnutrition and weight loss is worse, beyond the lack of response to anticancer treatments. Energy expenditure does not seem to be modified in cancer patients (25-30 kcal/kg), and therefore a reduced caloric intake leads to weight loss. Low values of a series of scores elaborated to quantify nutritional conditions have confirmed that survival is lower in patients with malnutrition. Patients with malnutrition are more affected by surgical complications and show a worse response to treatments in terms of toxicity. Nutritional support is therefore fundamental, both for the choice of timing and methods of nutrient administration in relation to different clinical conditions. The best results are in fact obtained in the mild forms of malnutrition (precachexia). Weight loss, if detected early and treated, can be slowed down by allowing anticancer treatments (1).

Assessment

For an assessment of the risk of malnutrition and prognostic factors, some validated measures have been suggested (table 1), which refer to simple parameters such as body mass index, BMI, C reactive protein (PCR), albumin, and weight changes over time (2).

-Prognostic nutritional index	10×serum albumin [g/dL])+(0.005×lymphocytes/μL). ≤45 = severe nutritional deficit
-Glasgow prognostic score	PCR ≤10 mg/l - albumina ≥ 35 g/l = 0 PCR >10 mg/l = 1 albumin <35 g/l =1
-ESPEN NRS 2002 if BMI <20.5:	
Mild = 1	Weight loss >5% in 3 months or decreased intake <50-75%
Moderate = 2	Weight loss >5% in 2 months or BMI 18.5-20 and clinical worsening or decreased intake 25-50%
Severe = 3	Weight loss >5% in 1 month (>15% in 3 months) or BMI <18.5 and clinical worsening or decreased intake 0-25%

Table 1 Nutritional prognostic indexes

The effectiveness of nutritional measures depends very much on the stage of the disease. In patients under treatment and with a good performance score, early treatment may allow an improvement in nutritional status, which remains unlikely in advanced patients. The ways to provide nutritional support include the oral, enteral, and parenteral route (3). An initial step includes an explanation and communication of the situation, and dietary suggestions to encourage an increase in the calories introduced (smaller meals multiplied in the day, choice of nutrients). It has been observed that dietary advice offers good results on nutritional status (4) and that the addition of nutritional support allows weight gain and improves some aspects of quality of life (5). The results also depend on the patient's psychological status and his ability to collaborate (6). Oral supplements are probably the most frequent treatment suggested, often together with dietary advice. The supplements serve to increase the introduction of calories or some nutrients in particular, such as proteins, correcting the current diet or replacing it.

The main indications are mild forms of malnutrition, in patients who are candidates for treatment that are likely to cause gastrointestinal symptoms or mucosal lesions. The patient should be able to swallow. Overall, the results seem to improve nutritional indices, although not in the long term. With regard to palatability, preference seems to go to elementary supplements rather than peptides. Some supplements are enriched with fatty acids, which would have an anti-inflammatory

function. The effects, although promising, are still controversial. Branched-chain amino acids have long been used as supplements for stimulation on the hypothalamic axis of the serotoninergic type with a competitive action of cerebral passage towards other amino acids such as tryptophan, or accelerating the synthesis of proteins. The use of fish oil or ω3 polyunsaturated fats has been suggested for their protective anti-inflammatory power, even if current evidence is insufficient. Overall, in advanced patients the benefits of using food supplements seem to be minimal.

In patients with manifest malnutrition in which it is not possible to use the oral route, for example in head and neck tumors, enteral nutrition may temporarily replace feeding via the nasogastric probe or gastrostomy. The evidence of the effectiveness of this treatment in terms of nutritional benefits and survival is not substantial. It is believed that parenteral nutrition can provide a greater caloric amount. Parenteral nutrition, however, encourages intestinal atrophy and bacterial translocation due to the absence of nutrients in the lumen. Parenteral nutrition should be used in patients in whom the gastrointestinal tract is not functioning (preperitoneal carcinosis, post-treatment diarrhea). Many studies have highlighted the costs and complications of parenteral feeding. It should be noted that many innovations have changed clinical nutrition in recent years, further increasing costs ("all-in-one bag" nutritional bags, new enteral and parenteral formulas), but minimizing the risks of complications (hygienic standards, operator education).

The use of parenteral nutrition is not recommended during treatment unless serious and long lasting gastrointestinal toxicity is evident, especially in patients undergoing bone marrow transplantation (7). In a recent meta-analysis, it was confirmed that parenteral nutrition causes an increase in the incidence of infections and other metabolic complications and does not prolong survival compared to enteral nutrition (8). The use of parenteral nutrition in advanced patients is even more controversial. The most frequent indication is the presence of a sub-obstruction that does not allow oral or enteral feeding (9). The choice should fall only on patients who have a certain expectation (2-3 months) in which intestinal transit is compromised (2). In the terminal phases or in case of failure, any parenteral nutrition should be discontinued. The bioethical and communicational aspects of nutrition in advanced patients have been discussed in chapters 2 and 3.

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CHAPTER TWENTY-THREE F

DEHYDRATION

Dehydration is a state in which there is a negative net balance of the amount of water and/or electrolytes. The body fluid deficiency includes a state of dehydration, in which fluid deficiency is predominantly intracellular and is associated with hypernatremia, and a state of plasma volume depletion in which a reduction of intravascular volume is observed with conditions of isotonia, hyponatremia, or hypernatremia. There are many causes that lead to dehydration, due to a decrease in fluid intake due to clinical conditions involving a restriction of liquids, or situations in which liquid losses are observed (table 1).

Decreased intake	Increase in losses
Anorexia	Short bowel
Cognitive alterations	Diarrhea
Depression	Enteric fistulae
Dysphagia	Fever
Nausea	Vomiting

Table 1. Causes of water deficit due to decreased intake or increased fluid losses

While it is difficult to calculate the amount of fluid introduced, in patients with anorexia, nausea, dysphagia, depression, or cognitive deficit in which the sensation of thirst is often lost, it is likely that the intake is not sufficient. From the clinical point of view there are numerous signs associated with dehydration, such as changes in cognitive status, fatigue, thirst, nausea, and xerostomia, which can be associated, in the most intense forms, with reduction of skin turgidity, hypotension, and tachycardia. These signs may however be present for other reasons associated with the state of advanced disease. From the biochemical point of view it is common to observe an increase in urea, creatinine, hematocrit, and natremia (1).

Treatment

Beyond the correction of certain factors leading to dehydration and the associated symptoms, adequate oral water support is essential. During critical phases of the disease, intravenous hydration is essential for the recovery of the patient's condition. In particularly dehydrated patients with decreased diuresis, hydration with solutions containing electrolytes and the use of plasma-expanders allow a rapid recovery and correction of the main biochemical parameters which correspond to an improvement of diuresis and clinical recovery (table 2).

In the advanced patient with a short expected survival, there are many controversies about the need to rehydrate the patient, which are based on the advantages and disadvantages of forced hydration. Maintaining adequate hydration allows a better control of symptoms, especially in patients with cognitive disorders, which can be aggravated or induced by dehydration. Moreover, hydration from the communication point of view is considered a standard of care perceived positively by patients and family members (2-4). There are some anedoctal considerations that have been historically perpetrated but never demonstrated (table 2).

- symptoms of dehydration are less relevant in the comatose patient
- process of death is prolonged with a forced hydration
- patient care is facilitated for a lower production of urine
- gastrointestinal and respiratory secretions are diminished
- peripheral edema does not increase
- dehydration leads to a state of sedation
- parenteral hydration is a burden for the patient

Table 2. Anedoctal considerations against hydration at the end of life

Attempts to find correlations between biochemical alterations, hydration status, and clinical signs have resulted in inconclusive results (5). All these elements, beyond the more or less different professional attitudes, in some cases tend to be misleading because they do not take into account the circumstances and the clinical context. In fact, the attitude can be complementary and sequential in the treatment process, avoiding sterile conceptual exaggerations. In the literature, disproportionate quantities of liquids are reported in a hospital environment and the complete absence of hydration in hospices (6), as if hydration were an environmental problem, and not the identification of a precise technical requirement for the administration of fluids for the well-being of the

patient. In an acute palliative care unit, it has been reported that a hydration of about 1 liter a day improves sleepiness and myoclonus (7), while in the hospice environment the same treatment did not offer particular advantages compared to 100 ml/day. While there does not seem to be clear evidence of the need for hydration in the last week of life (8, 9), the risk is that patients with delirium, associated, facilitated, or induced by dehydration, are sedated as non-responsive patients, while adequate treatment of opioid toxicity and rehydration would have been able to make the clinical picture reversible. The scientific evidence remains thin (10). In these phases, therefore, the decision must be made individually on a case-by-case basis (8), considering also the prognostic factors of short survival. In table 3, therapeutic attitudes are reported, which can be sequential and complementary in different phases and circumstances. Discussion of hydration in the last days of life will be resumed in the chapter dedicated to palliative sedation (chapter 26). From a clinical point of view, intravenous hydration is preferable, especially in patients with long-term venous access, and in an acute setting. Alternatively, the subcutaneous route is frequently used in hospices or at home for ease of use. Hyaluronidase, if available, is able to promote the absorption of electrolyte solutions.

Hydration 1 l/day + gelatine 0.5-1 l/day Furosemide 20-40 mg/day	States of dehydration, oliguria Neurotoxicity by active opioid metabolites
Hydration 1000 ml/day	Standard therapy
Hydration 250 ml/day	Patients with expected survival <3 days or in cases of palliative sedation

Table 3. Different treatments according to different clinical circumstances

Finally, there are ethical considerations, already anticipated in chapters 2 and 3, which concern hydration and artificial nutrition, often confused in some ethical evaluations. Perceptions and cultural attitudes must be carefully considered in the communication of the possible benefits of the choice to hydrate or not. In some cases religious considerations can invalidate the final judgment (5).

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CHAPTER TWENTY-THREE G

ANEMIA

Anemia refers to a state in which there is a decrease in the number of red blood cells and a consequent insufficient release of oxygen to the tissues, producing a series of symptoms in cascade. Anemia is one of the most frequent complications in the cancer patient in the various stages of the disease (1). Erythropoiesis is a very delicate process regulated in such a way as to keep the circulating number of red blood cells constant. These cells require a special environment within the marrow to allow survival, proliferation, and differentiation. The pluripotent system has the capacity to self-replicate or to definitively differentiate itself. Some cells survive for a long time, while others cease to function and are replaced by the silent stem system. In addition, stem cells have the ability to respond to stressful situations where the demand for a certain line prevails. A series of hematopoietic growth factors is crucial in regulating these processes. Essential nutrients such as Fe ++, folate, and vitamin B12 are essential. Among the known growth factors, erythropoietin (EPO) is definitely the most important substance, functioning as a mitogen or as a survival factor depending on the stage of cell maturation. The production is constitutive or induced by a threshold of tissue hypoxia rather than the number of circulating erythrocytes. Therefore, it is necessary to have a significant reduction of red blood cells to stimulate the release of EPO. The increase in EPO is achieved by the recruitment of a greater number of renal interstitial tubular cells. The renal response to hypoxia is exponential for transcription of a gene. The EPO starts, at the bone marrow, to interact with highly specific receptors expressed on the progenitor cells that from that moment become dependent on the presence of EPO, since the binding increases the survival capacity to reach the reticulocytic phase (2).

The reduction of red blood cells can basically result from lower bone marrow production, increased destruction, or blood loss. There are many causes of anemia, including chronic hemorrhage in intestinal cancer, bone marrow metastases, and autoimmune hemolysis in hematological cancers or drug use. On the other hand, cancer is a thrombotic condition due to the high production of prothrombotic substances and this condition can lead to

the destruction of red blood cells. Patients undergoing chemotherapy and radiotherapy are at high risk for the suppression of hematopoiesis. Finally, malnutrition or the consequences of surgical procedures can limit the absorption of substances necessary for hematopoiesis. Anemia has also been classified according to cell indices. Microcytic anemia (MCV <80) is associated with iron deficiency, while macrocytic anemia (MCV> 100) is associated with vitamin B12 and folate deficiencies, hemolytic anemia, or liver cirrhosis. The normocytic forms are found in renal failure, in hypothyroidism, and in medullary aplasia. Beyond the value of hemoglobin, the presence of anemia is accompanied by a series of symptoms that weigh heavily in the general economy: decrease in activities and a shorter survival, even if it is difficult to establish whether it is a primary factor or just because associated with more advanced conditions or more aggressive disease. Fatigue is definitely the most striking symptom of accompaniment, even if the relationship with the hemoglobin values is not so simple and straightforward. The correction of anemia is potentially one of the few measures that make the symptom reversible (3).

Treatment

In a global assessment, possible correctable causes of anemia, such as nutritional deficiencies, should be considered. In renal failure where there is a reduction in EPO production, treatment is consequent. Red blood cell transfusion is a rapid and effective measure in restoring normal hemoglobin values. However, the symptomatic benefits on the state of well-being and on fatigue are generally transitory, when the primary causes persist(4). Transfusion is indicated in symptomatic and acute patients with values below 10 g/dL. In chronic anemic patients the indications are more restrictive (<8 g/dL). In advanced patients, transfusion is complicated and practical effects are not always evident. The benefits in terms of improving quality of life are always difficult to appreciate and not always correlated with the correction of the hemoglobin levels. Agents that stimulate erythropoiesis, such as EPO and its derivatives, are an option in the treatment of anemia, particularly in renal failure, where causative agents function (5). Also in this case there is no clear optimal threshold. For example, values> 13 g/dL are associated with higher mortality and thromboembolic risks. Although treatment with these agents may reduce the use of transfusions and improve quality of life, there are significant restrictions on the subject, and the indication is now being given to patients receiving myelosuppressive cancer therapy with

non-curative intent. In addition to these problems we must consider that only half of the patients are responsive and the timing requires a few weeks to have an effect (6).

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CHAPTER TWENTY-THREE H

PERIPHERAL EDEMA AND LYMPHEDEMA

Peripheral edema

In many clinical circumstances there is an accumulation of fluids whose pathophysiology is quite varied. Peripheral edema and lymphedema are the conditions most frequently observed in cancer patients, albeit in very different situations. Under normal conditions, the organism maintains the equilibrium between the hydrostatic pressure and the osmotic pressure at the level of the capillaries, which are equipped with partially permeable walls. Colloid-osmotic pressure is the pressure exerted by the solutes in a solution of the interstitial liquid and/or plasma, and depends on the concentration of proteins and minerals present in the biological liquids. In water-permeable vessels in which there is a higher concentration of ions and proteins there will be a greater colloid-osmotic pressure which will attract water molecules from the outside towards the inside of the membrane in order to eliminate the concentration difference of solutes as much as possible between the two membranes. In the capillaries and in the interstitial liquid the movement of the water is directed from the interstitial liquid to the capillaries thanks to the difference in oncotic pressure between the two sectors and the difference in hydrostatic pressure. In arterioles there is a tendency to the diffusion of liquids towards the interstitial liquid, due to a higher capillary hydrostatic pressure with respect to the oncotic pressure. In the venules, on the contrary, the hydrostatic pressure is lower than the oncotic pressure due to the low speed of the pulsating venous flow. Therefore, there will be a tendency to move from interstitial space to the venules. In the presence of an imbalance of homeostatic forces that maintain normality, we observe the discharge of liquids from the capillaries. Increased hydrostatic pressure in venous circle can be observed in deep vein thrombosis or heart failure.

Oncotic pressure (that is, the pressure exerted by the colloidal components of the blood, in particular proteins) can instead change the flow of fluids at the capillary level. A decrease in oncotic pressure may be due to malnutrition and renal or hepatic dysfunction altering plasma

protein content (especially albumin concentration) (1). Inflammatory processes can also alter the permeability of capillaries. A particular systemic inflammatory process is typically represented by advanced oncological disease, in which there is a loss of capillary permeability associated with biochemical variations, such as a hypoalbuminemia, and a lack of mobilization favoring the appearance of peripheral edema. The accumulation of fluids may also occur due to a lack of absorption of the same, which generally is associated with an obstruction of the venous and lymphatic vessels due to the extrinsic compression of a neoplastic mass, which determines a peripheral edema underlying the obstruction (2). Peripheral edema may evolve and generalize, extending to the abdomen and thorax, or to the periorbital area. The generalized edema forms have as main causes decompensated heart diseases, diseases that cause severe renal failure, pathologies that cause a significant reduction of albumin, such as nephrotic syndrome, severe impairment of liver function, or states of severe nutritional deficit. Some medications (calcium antagonists, opioids, gabapentin) may also produce the appearance of a peripheral edema as a side effect.

Treatment

Once the basic pathology has been identified, the most correct therapy for peripheral edema can be established. Diuretics, in particular furosemide, are the most common drugs used with this purpose. Corticosteroids may be useful in the forms of compression at the iliac-femoral vessels. The use of hypertonic solutions is very effective, in particular for the speed of the effect. This treatment is based on the osmotic attraction of the liquids accumulated within the bloodstream by a rapidly administered hypertonic solution. The liquids returned to circulation are subsequently eliminated by a relevant dose of furosemide. It provides a bolus of hypertonic solution (60 mEq of sodium chloride in 150 ml of saline, administered in 30 minutes), followed by furosemide 250 mg. Two administrations a day for two-three days allows the remotion of large amounts of accumulated water. Subsequently, the use of furosemide 40-60 mg will be given to prevent further formation of liquids (3). It has also been proposed to drain fluids to the lower limbs by the placement of drainage bags and pouches, even though this solution seems to be quite invasive (4). The use of albumin is not recommended in the forms of systemic inflammation, in which the result could be even worse from the oncotic point of view due to the passage of albumin into extracellular fluids. In the forms of cardiac and hepatic heart failure the mechanism will

be supported with a consequential treatment. Maintaining an adequate level of hydration will be individualized according to clinical needs (5).

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Lymphedema

Lymphedema is one of the most significant problems for patients who have recovered from cancer. The exact incidence in long-term breast cancer survivors varies widely (6-23%) depending on the type of treatment performed. Axillary dissection is definitely the most burdensome intervention. Melanoma, operated gynecological tumors, and head-neck tumors are other conditions frequently associated with lymphedema. This condition impairs quality of life in its physical, emotional, and social aspects (1). Lymphedema also involves a psychological condition of distress, due to the alteration of one's appearance, with influences also on the sexual sphere (see chapter 23l). Lymphedema develops due to an imbalance between the venous micro-vascular filtration and the capacity of the lymphatic drainage system. Vascular abnormalities leading to lymphedema formation include vasodilation and/or angiogenesis, which may increase vascular flow not compensated by existing lymphatic structures. Lymphedema may result from an inherent blockage of the lymphatic system or damage produced on the lymphatic vessels or lymph nodes. The second form is the most common and is typically caused by an outflow obstruction or a lymphatic vessel injury resulting from surgery,

radiation, trauma, and infections (2). Obesity is a well-known risk factor in oncology, although the mechanism remains unclear.

The lymphatic system is a complex network consisting of lymph node stations, located in various locations (armpit, groin, neck, abdomen), and by lymphatic vessels that flow from the periphery into trunks of greater caliber. The lymph flows through the lymphatic vessels and lymph nodes. In fact, the lymphatic system provides a drainage system to convey excess fluids produced by the tissues towards the venous circulation. Furthermore, the lymph nodes act as a filter by incorporating and interacting through the lymphocytes with various substances including infectious agents and neoplastic cells. Lymphedema manifests itself as a swelling due to the accumulation of lymph in the tissues. It can affect the upper limb (after surgery and/or radiotherapy for breast cancer with involvement of the axilla) or the lower limb (for example, after surgery and/or radiotherapy to the inguinal lymph nodes for gynecological tumors – uterus, cervix, ovary, or vulva – or because of a melanoma) and sometimes also other parts of the body if the regional lymph nodes have been surgically removed or subjected to radiotherapy, or are blocked by the tumor. If the lymph nodes or lymphatic vessels are compromised or obstructed by a fibrotic or compressive phenomenon, the lymph cannot drain and consequently determines the typical swelling. The skin of the affected limb has no change in color and temperature, unless it is associated with an infection. Over time, without proper treatment, it tends to harden (3).

Lymphedema develops within weeks, months, or years after anti-tumor treatment. Generally it is not accompanied by pain, but a sensation of progressive heaviness up to the presenting of difficulties in carrying out daily activities. Lymphedema only appears in 20 to 30% of patients, and generally in modest form following surgery or radiotherapy. The risk increases in the case of combined treatment, as in the case of breast cancer. Lymphedema is an irreversible condition, although it can be mitigated by timely treatments. Patients who undergo surgery for the removal of axillary or inguinal lymph nodes and/or radiotherapy and those undergoing surgery followed by radiotherapy in a lymph node district have a higher risk of developing lymphedema (4) (table 1).

Lymphadenectomy
Radiotherapy
Tumor infiltration
Extrinsic compression from adjacent tumor

Table 1. Causes of lymphedema

Infections, which are a stimulus for the production of lymph, can exacerbate the risk under these conditions. In the limb or an area in which a lymphedema is developing, swelling, change in touch, skin changes (turgidity, dryness), and pain appear. At first the swelling is mild and often unnoticed, and then a fovea can be observed, while in the more advanced phases, the skin and its layers harden and lesions may appear with loss of lymph and deformation of the limb which causes great limitations in the function.

Assessment

There are numerous measurement tools. These measurements will be repeated over time for an evaluation of the effectiveness of a treatment. Measuring the circumference of the extremities is perhaps the simplest method. The infrared light perimeter allows us to visualize the area and measure it with greater precision. Bioelectrical impedance measures the opposition to the flow of an electric current (5).

Treatment

The causes of lymphedema are irreversible, and therefore the treatment aims to reduce the volume of the affected limb and improve its function, relieve symptoms, and prevent further stagnation of lymph and the onset of infections. Following the treatment, the swelling should be reduced and the symptoms should improve, but in some cases it may take weeks or months before noticing a real improvement. For greater effectiveness, these treatments will have to be precocious, constant, and continuous (3, 4) (table 2).

- skin care to prevent injuries and infections
- lymphatic drainage to facilitate the outflow of the lymph
- content therapy with application of elastic-compressive guardians and compression bandages
- motor therapy with specific exercises to improve the flow of lymph and promote drainage
- pressotherapy
- deep breathing exercises to be included in the daily routine
- weight control

Table 2. Lymphedema treatments

Even a minimal lesion represents a potential access point for bacterial agents. In fact, the lymph is particularly rich in proteins and represents a suitable ground for the development of infectious agents. Lymphedema also tends to dehydrate the skin. Pruritus increases the risk of self-injury and consequent cracking. Deep daily hygiene, through the cleaning of skin folds and a constant hydration of the skin, can bring relief and prevent the onset of infections. The skin should be protected with suitable and not tight clothing, with sunscreen, avoiding exposure to heat sources, and using insect repellents. Hair removal or nail care must also be careful. Equally important is to protect the risky arm or leg in daily activities that can produce skin lesions (wearing gloves or suitable clothing). Slight physical exercises help restore the function of the arm or leg after surgery and/or radiotherapy. This rehabilitative therapy is very important for recovery. The exercises should be performed gradually, consistently, and regularly, because they preserve the elasticity of the joints and muscles. Being overweight is an additional risk to be prevented by an adequate diet (4).

Lymphatic drainage is a very important massage technique for the treatment of lymphedema, because it promotes the reabsorption of the lymph collected in the edematous area or in the outflow towards another area (6). Lymph drainage is usually combined with containment therapy to maintain effects over time, but is essential in areas where containment therapy is difficult to apply, such as the head and neck. Each session, performed by a technician, is generally completed with the application of a multi-layered elasto-compressive bandage to be kept in place for at least 10-12 hours and to be renewed after each session. It can also be done in simple form at home with appropriate training. It is advisable before lymphatic drainage to perform breathing exercises to promote the drainage of the lymph (7).

Containment therapy is carried out with an application of elastic-compressive guardians or bandages. The brace exercises a graduated compression on the limb to facilitate the drainage of the lymph and prevent further collection, stimulates the drainage of the lymph from the hand or foot into the armpit or the groin, and enhances the activity of the muscle pump. The brace should be of appropriate size and with a compression gradient measured on the characteristics of lymphedema. Various tutors are available (pre-made or made to measure) and models (bracelets, gloves, tights, knee-highs). The brace should be well tolerated and put on in the morning on a less swollen limb and kept on for the daytime hours. An elasto-compression bandage is applied at the end of each manual or mechanical therapy session. If well tolerated, the bandage

must remain in place for 18-20 hours. It generally allows the performance of daily activities and its action is particularly effective when the limb is kept in motion (8). With appropriate training it is advisable to pack the bandage at home.

Pressure therapy is a mechanical technique that uses equipment through multi-chamber sleeves that swell and deflate progressively, creating a compression wave from the bottom up that favors the ascent of the lymph. The effectiveness of pressure therapy increases when it is performed after lymph drainage and is then followed by the compression bandage. Being overweight slows lymphatic circulation and makes treatment more difficult. It is good, therefore, to check weight and put in place an appropriate diet (4).

Physical exercise promotes lymphatic circulation through the muscle pump, and improves mood and compliance with treatment (9). Techniques such as yoga or stretching and breathing techniques are preferable. The exercises should preferably be done in the morning with gradualness and continuity, wearing the brace. Some self-massage exercises, aimed at favoring the emptying of the lymph node chains involved in the central direction, generally favoring gravity, can be beneficial.

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CHAPTER TWENTY-THREE I

SKIN LESIONS

The skin has an important symbolic meaning for the patient because the lesions are visually evident and perceived by the patient directly, compared to for example the disease, and represent a strong psychological distress. The skin can be directly involved by the tumor and the consequent visual disfigurement is associated with a deterioration in quality of life. The most common tumors involving the cutaneous tissue are melanoma and breast cancer (1). Treatments can also lead to significant skin lesions, such as in actinic dermatitis, both in acute and delayed form. These forms depend on the extent of irradiation and on individual sensitivity. The edema and redness are evident in the acute phase, up to the desquamation and erosion of the skin. The chronic form arises after a few months due to vascular damage (2). Lesions from chemotherapeutic agents are very frequent and present themselves in the form of alopecia, nail injuries, and skin reactions to the hands and feet up to the more evident forms of graft versus host disease, which appears after an allograft of stem cells. It is characterized by a lichenoid eruption and an erythema-papular rash that leaves the pigmented skin up to the dermal fibrosis, with loss of adnexal functions. There are paraneoplastic forms that present themselves as dermatomyositis (for example in melanoma and lymphoma).

The appearance of skin lesions in the cancer patient is a disturbing event for conditions associated with the disease and treatment, such as immunosuppression, infections, edema, previous tissue irradiation, malnutrition, dehydration, neuropathy, old age, entrapment, and a series of concomitant diseases that make treatment and recovery difficult. From a psychological point of view, skin lesions from bedsores are a serious burden for the patient who feels and sees his body deteriorate. The decubitus ulcer is a lesion of the skin and underlying tissues, generally along a protruding bone surface. The coccyx, the sacrum, and the hip are the most frequent sites due to the limited presence of fatty tissue in these sites. These lesions are classified by stages that emphasize the extent of the lesion through the various skin layers (table 1).

Stage 1	Stage 2	Stage 3	Stage 4
Intact, reddened, unmodifiable with pressure	Dermal thinning with a superficial ulcer	Loss of tissue without exposure of bones, muscles, etc.	Loss of tissue without exposure of bones, muscles, etc. Presence of exudation and eschar

Table 1. Stages of progression of decubitus ulcers

The friction of extrinsic elements on the most superficial layers exacerbates the effects of pressure on the skin, for example in the case of dragging the patient rather than gently lifting him on the bed. Moisture by transpiration or the presence of liquids (due to incontinence, for example) are local aggravating factors. There are non-stageable forms in which the tissue thickness is lost, as the base of the ulcer is covered by necrotic material or an eschar. Until the material or eschar is removed, the injury stage cannot be established. Stable eschars, dry and adherent, without edema or fluctuation, are natural protections that should not be removed. Lesions progress rapidly if not drawn or if concausal factors persist. The poor peripheral perfusion in the dying greatly accelerates the progression towards the last stages of the ulcer. Skin lesions may also have other origins, such as vascular disease or diabetes, burns or trauma. Therefore a global view of the patient, regarding the initial causes, the evolution, and the concausal factors of a lesion, is fundamental. An objective examination must take into consideration the parameters shown in table 2.

- Site
- Depth and dimensions
- Presence of edema
- Conditions of the surrounding area and color, temperature and color
- Quantity and quality of secretions
- Pain

Table 2. Parameters to be evaluated in skin lesions

Prevention

The best treatment is prevention with a risk assessment, for example with the Braden scale, which examines six parameters: sensory perception,

skin moisture, degree of physical activity, ability to control and change the position of the body, feeding, friction, and sliding. Sensory perception is understood as the ability to respond adequately to the inconvenience associated with compression. The activity level should be considered as the level of physical activity. Mobility means the ability to change and control body positions. The friction-tension parameter is often underestimated. The patient, frequently, is moved by the family in an incorrect and inadequate way, being dragged rather than relieved, resulting in damage to the skin and underlying structures. The score to be given to each parameter ranges from 1 to 4, except for the friction-traction parameter, which goes from 1 to 3. A score of less than or equal to 16 is indicative of risk of decubitus ulcers (3).

Sensory perception	not limited	partially limited	very limited	completely limited
Humidity	rarely	occasionally	often	permanently
Activity	often walks	occasionally	in a bedded chair	bedridden
Mobility	not limited	partially limited	much limited	absent
Nutrition	excellent	adequate	inadequate	poor
Friction	absent	potential	present	slip

Table 3. Braden scale

Once the risk has been identified or the level of gravity has been diagnosed, preventive measures must be implemented in a realistic manner, according to the patient's conditions. They include providing for a daily inspection of a toilet with neutral soaps; the application of barriers for feces, urine and perspiration protection, possibly considering the use of absorbents for incontinent patients; and prevention of clutches on the skin using means to lift the patient, without dragging, and the application of lubricants, light coatings, or protectors of the elbows and heels. Mobilization in relation to the patient's abilities will be encouraged. One of the most important measures is the reduction of pressure on the tissues that is obtained by repositioning the patient often, both on the bed and in the wheelchair, protecting the trochanters, possibly using soft supports, avoiding massaging of the affected areas, and not using belts or rings that concentrate the pressure in small areas or sheepskin, which cannot reduce

the pressure. The nutritional status is another important factor to follow in terms of quality and quantity of nutrients and calories introduced, possibly following some laboratory parameters, including some markers of malnutrition (albumin, transferrin, lymphocytes) (4).

Treatment

The main purpose, often unrealistic for the large number of contributory factors, is the healing of the skin lesion. Prevention of the aggravation of lesions is already a good goal, with the treatment of pain, bad smell, itching, bleeding, and exudates. Beyond the described prevention measures, the control of the consequences of incontinence should be facilitated by a frequent toilet after each episode with the application of protective barrier substances on the skin (creams, oils, films). The absorbents should be kept at a certain distance, avoiding the trapping and maceration of the skin. Urine collection means (condom or urinary catheter) can avoid skin maceration in the presence of incontinence or frequent urination. There are similar means also to limit stool release. The correction of nutritional deficiencies, where possible, is a fundamental measure to prevent aggravation and allow the improvement of lesions (5).

Injury care must be simplified to make it frequent and manageable. The aim is to maintain a favorable environment, prevent infections, eliminate damaged tissue, promote wound closure, and protect against excess moisture (3). Wound care is designed to keep the affected site warm, dry, clean, and protected. Hot saline solution should be the most useful, least expensive, and most readily available cleanser for the toilet, either by irrigation or through gently placed sponges on the lesion. Bad smell, caused by tissue necrosis and infections, is one of the most troublesome problems. The removal of necrotic material often requires surgery or a forced, very painful removal, which should be assisted by appropriate sedation and analgesia. There are enzyme substances containing proteases which can facilitate the removal and dissolving of the necrotic material. It is more likely to occlude the lesion after applying proteolytic gel. It is a slow but effective and painless measure. Dry, stable, and dark heel excretion should not be treated if the site is not edematous, non-fluctuating, and not suppurated. Surgery should be recommended in type 3-4 lesions that do not respond to conservative treatment, only after assessing the benefits in relation to expected survival. If an infection is suspected, a culture could target the subsequent treatment, particularly for mycotic overinfections in malignant local lesions (4). The area of the lesion should be covered by a lining. The frequency of the change of

coating should be programmed in relation to the extent of the lesion but also to the burden for the patient because it is a painful operation that may require an analgesic intervention. The alginate absorbs large volumes of exudate. A charcoal or silver ion coating filters the malodorous or infected exudate. The choice of products and procedures will be reassessed over time in relation to realistic goals, and the stress associated with patient dressings (6).

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CHAPTER TWENTY-THREE J

FEVER - INFECTIONS

Cancer patients have a high risk of infection for the disease itself and its complications, the use of bladder or venous catheters, poor nutritional conditions, immunosuppressive treatments, viral infections, and the use of corticosteroids. In the advanced stages of the disease many of these factors coexist. Infections of the urinary tract, respiratory tract, oral cavity, and skin are the most common forms. The most frequently involved microorganisms are E.coli, Staphylococcus aureus, and Enterococcus (1). In patients with long-lasting central venous catheters, bacterial blood multiplication is frequent due to improper handling of the exit area. Fever is the typical sign of an infection, although it often does not have an infectious origin, and often the clinical picture is confounded by the concomitant use of drugs such as anti-inflammatory drugs.

Assessment

The assessment includes a hematological profile, the search for the site and the microrganism in question, with pharyngeal, pulmonary, urinary, blood, fecal, and liquor cultures according to the suspicion of the main site of infection. A radiological study of the thorax can confirm a diagnosis of airway engagement. A frequent re-evaluation is required in patients with neutropenia, multiple sites of infection, and multiple isolated microorganisms. In some patients this investigative burden is not always justified in relation to the limited survival. The decision will therefore be linked to a more global consideration of the patient's condition, expectations, and level of communication. In some cases, an infectious cause for fever is not evident. In this case a paraneoplastic form or the central involvement of the thermoregulation centers is more probable.

Traditional biomarkers, including C-reactive protein, leukocytes, erythrocyte sedimentation rate, and clinical signs and symptoms, are not specific enough to guide treatment decisions in infectious febrile diseases. Procalcitonin is a so-called acute phase reactant, rising in response to tissue inflammation and injury. Procalcitonin is normally secreted by the

lungs, intestines, and other tissues in increasing amounts in response to bacterial endotoxin in the bloodstream. A growing body of evidence supports the use of procalcitonin as a marker to improve the diagnosis of bacterial infections and to guide antibiotic therapy. Procalcitonin can be detected in blood within 2 to 4 hours of infection and peaks between 6 and 24 hours. It is used in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients and to help health care providers determine if antibiotic treatment should be started or stopped in patients with lower respiratory tract infections.

Thus procalcitonin levels may help diagnose and identify serious bacterial infections and to distinguish between bacterial and non-bacterial conditions, and guide antibiotic treatment.

Procalcitonin, however, lacks sufficient precision as a stand-alone method to diagnose or rule out infection, and must always be considered in context with individualized clinical decision-making (2).

Treatment

While in patients receiving anticancer treatments the use of antibiotics, possibly after isolating the responsible germ with the appropriate samples in the affected sites (urine, bronchial secretion), is inevitable, the use of antimicrobial drugs is rather controversial in advanced patients, and is mainly directed at symptom control (3). Often, but to varying degrees, some investigations are avoided in order not to increase the distress load for the patient. Studies to suggest how to intervene are quite limited. While an intensive approach to reduce morbidity and mortality is required in the acute setting during cancer or postoperative treatment, in advanced cancer patients with short survival the aims are predominantly symptomatic and should be balanced with the expected and limited benefits of antibiotic therapy (4, 5). In general, even if using targeted antibiotics, in this phase the clinical response is not exceptional, probably due to the concomitant presence of other unfavorable conditions, such as the state of immunosuppression, malnutrition, the decrease in the level of consciousness, and immobility. While responses to antibiotic treatment in the presence of urinary infections are more likely, respiratory tract infections appear to be more resistant. Sulfonamides are well tolerated and effective in a few days for urinary tract infections. For bronchopneumonia, macrolides can be a good solution for their broad spectrum of action (see table 1).

Site	Signs, symptoms	Investigations	Antibiotics
Urinary tract	dysuria, fever, pain	urine, culture, antibiogram	sulphonamides, levofloxacine
Oral cavity	mucositis, pain, fever	oral smear, culture	fluconazole
Respiratory tract	cough, dyspnea, fever	secretions, culture, Xr, CT	macrolides, levofloxacin
Sepsis	fever, hypotension, confusion, tachycardia	blood culture	cefalosporines, aminoglicosides vancomycin

Table 1. Most frequent infection sites, signs and symptoms, investigations, and antibiotics

However, survival does not seem to be strongly influenced by the presence of infections or by antibiotic treatment (6, 7), and the data are quite controversial and not very definitive (3, 8). Therefore, the decision to undertake or continue antibiotic treatment must be discussed and shared with the patient and the relatives, who must be made aware of the aims of the treatment according to the clinical conditions and the progress of the disease. Therefore the treatment must be individualized on a case by case basis, considering the chances of success in a given context and the expected survival. The symptomatic use of common antipyretics is probably justified in most cases. The use of corticosteroids or paracetamol is taken into account in the forms in which the febrile situation is likely to be charged to paraneoplastic or central fever forms.

A very particular form is represented by febrile neutropenia. Neutropenia is commonly seen as an effect of cytotoxic therapy, although in some cases it is the disease itself that interferes with hematopoiesis, as in the case of leukemia. For most chemotherapy treatments with myelotoxic potential, neutropenia nadir appears between 5 and 10 days, whereas for more intense regimens, for example those used for hematological diseases, neutropenia appears much more intense and lasting (9). Anthracyclines, taxanes, topoisomerase inhibitors, cyclophosphamide, and ifosfamide are the drugs with a strong neutropenic action. Risk factors are represented by the short latency in the appearance of neutrophilia, from exposure to previous treatments, concomitant immunosuppression, increases in alkaline phosphatase, bilirubin, transaminases, reduction of glomerular filtrate, and the presence of cardiovascular comorbidity (10). Only in a small number of cases is it possible to isolate an infectious agent. Gram-positive are responsible for

most cultures and include staphylococcus aureus and epidermidis, especially in patients with central venous catheters, streptococcus pneumoniae, streptococcus pyogenes, streptococci viridans, and enterococcus faecalis. Among the positive GRAMs, the most frequent is the corynebacterium. Among GRAM-negative, instead escherichia coli, klebsiella species, and pseudomonas aeruginosa prevail. Candida is the most frequent fungal infection, while aspergillus and zygomycetes are the most feared for their invasiveness (11).

Infection is the most frequent cause of febrile neutropenia. Because of the non-inflammatory reaction, peripheral signs are often associated with the skin, in the form of erythema or abscesses. A pneumonic outbreak is often observed. Under values of 500/mm^3 the patient is considered neutropenic. Vulnerability to infections also exists with values below 1000/mm^3. The risk worsens with lower values. At least 20% of patients with values below 100/mm^3 have a bacteremia (12). The physical examination will highlight mucosal and cutaneous lesions or lesions in the catheter sites. At least blood cultures should be performed, one of which from the central catheter site if present. A more premature positivity from the central line suggests that the source of the infection is the catheter (13). Urinalysis and a thoracic radiogram complete the initial investigations. An empirical treatment is justified because with its timeliness it can prevent a fatal evolution in many cases. The specific coverage can be made upon arrival of the laboratory data. Eventual corrections allow further improvement of the prognosis. Those with values below 100/mm^3 or with progressively worsening clinical conditions with suspected pneumonia are considered high-risk patients. A broad-spectrum antibiotic with a cephalosporin or carbapenem monotherapy is the recommended antibiotic regimen. Vancomycin, indicated above all for catheter infections, should however not be administered as monotherapy. Ciprofloxacin and amoxicillin may be used in patients at low risk where neutrophil resurfacing is expected within a few days. If the fever persists for more than two days the patient should be hospitalized. Therapy should be continued at least until the erythrocyte count is improved (5 million/μL)). Combination with antifungals should be considered for high-risk patients who remain febrile after a week of broad-spectrum antibiotics without detection of the infectious cause (13).

The diagnosis of an infected catheter does not necessarily require removal, especially if the cause is a staphylococcus, although persistence may lengthen response times. For an infection with staphylococcus aureus, pseudomonas aeruginosa, or mycetes, the catheter will be removed and prolonged antibiotic therapy will be given for two weeks (14). Growth

factors should not be given regularly to all patients with febrile neutropenia (15). Prophylactic use, however, determines a benefit in patients at risk. Growth factors should therefore be administered in patients who have had febrile neutropenia in previous cycles. The use of granulocytes is considered necessary only in patients with bronchial pneumonia and prolonged neutropenia in patients undergoing bone marrow transplantation (16).

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CHAPTER TWENTY-THREE K

VENOUS ACCESS

The treatment of the cancer patient requires stable venous access to be used in many circumstances, including chemotherapy, the administration of blood products and antibiotics, parenteral nutrition, emergency treatment, and any blood samples (1). The presence of a central venous catheter (CVC) prevents anxiety relating to venipuncture.

There are a number of available systems: tunnellized catheters with subcutaneous cuffs, ports, and peripherally implanted catheters (PICCs). All CVCs have potential acute complications, such as bleeding, malposition, cardiac arrhythmias, pneumothorax, and other late complications, such as infection, thrombosis, and malfunction.

Administration of multiple drugs at the same time
Parenteral nutrition
Prolonged and frequent treatments
Extended treatments at home
Prevention of vesicant chemotherapy injuries

Table 1. Indications for a CVC

The need and the choice of the type of CVC will depend on various factors, such as prolonged treatments, cycles of chemotherapy with potentially stinging drugs, availability in the patient of peripheral veins, reduced costs, preferences. Peripheral teflon venous catheters can remain in place only a few days. They then require repetition of the puncture in an alternative site. Central venous catheters are larger in size and are positioned after a venipuncture of a large vein in the thorax, neck, or limbs. These catheters can stay in situ for months. Each type of catheter has its indications and contraindications, costs, and complexity, and the choice must fall on a series of evaluations that have to be applied to the individual case. The puncture of the vessel through use of a needle involves the advancement of a thin metal guide, and after the removal of

the needle, the sliding of the catheter around the guide to the intended seat, followed by the removal of the guide.

The port a cath is a central venous system implanted in a subcutaneous thoracic cavity (figure 1A). It is generally preferred by the patient as it does not affect the normal habits of daily life. It guarantees a lower percentage of infections (in the order of 6%) compared to other external systems as it minimizes the possibility of contamination with the outside. The port is not ideal for blood transfusions and blood samples, especially due to the size of the needle, which acts as a link between the inner chamber and the outside. The port is implanted with a minimally invasive surgery. The system is characterized by a button of about 3 cm in diameter with a raised central surface, which will be visible under the skin, where one can insert the needle for the administration of the drug (which accesses the bloodstream through a flexible tube, called a catheter, which is inserted directly into the subclavian vein). The button, known as a reservoir, is placed in the upper part of the thorax below the clavicle. The external needle is removed at the end of the infusion, after washing with saline solution and heparin to avoid the occlusion. No daily maintenance is required. Theoretically, it could be left in place for years, if well maintained hygienically. Periodic washings with 30-day deadlines are sufficient during the period in which the patient does not receive therapy. Among the most frequent complications are skin ulcerations, local infections, seromas, and errors in the puncture of the chamber.

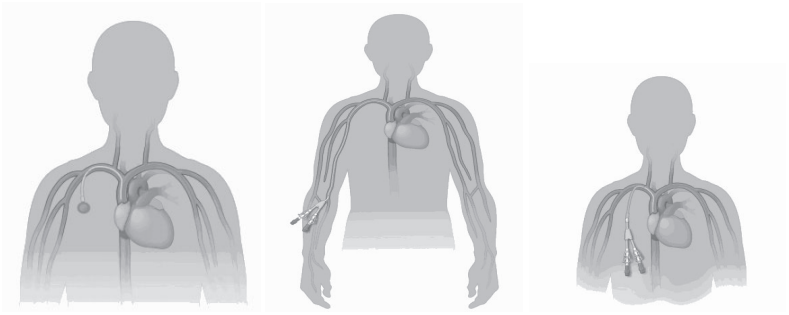

Figure 1. A = port, B = PICC, C = traditional CVC

The PICC is introduced through a vein in the arm and advanced into the superior vena cava up to the entrance to the atrium (figure 1B). The procedure is ultrasound-guided, can be performed by a PICC nursing team, and can also be used in patients with coagulation disorders. A PICC can remain a few months and remains fixed to the arm thanks to a special

adhesive. Compared to the common PICC, the midline is shorter. For both catheters it is necessary to carry out periodic washing and hygiene, and to cover during bathing or showering.

Traditional CVCs, placed in a jugular or subclavian vein, can be tunneled subcutaneously and exit directly from the skin (figure 1C). Their fixing can be facilitated by an adhesive cap in the subcutaneous tissue. The catheter can be used for months. It requires periodic washing and cleaning. It is not recommended in patients with tracheostomies or patients highly compromised from the immunological point of view.

The Groshong catheter is a central venous catheter with a tunneled silicone catheter, provided with a dacron cuff, a distal antireflux valve, with a closed tip, which protrudes from the skin. It is available in different calibers and with a double pathway (figure 1C).

The Hickman catheter is an open-ended, tunneled silicone catheter. Unlike the port, it has the advantage of being more easily implantable, at lower cost, easy to manage, does not cause decubitus, and does not need heparinization. Among the main disadvantages are a greater compromise of lifestyle (it alters the body image), the need of periodic dressings, the risk of getting easily infected or occluded, or inducing a venous thrombosis, and the limited duration. This system requires frequent medications of the catheter exit (approximately once a week) and washing with saline solution after each use. Beyond acute complications during puncture and catheter insertion, many late complications can be observed with the use of the chosen system, such as local infection, systemic infection, injury, kneeling, and catheter obstructions. The nursing procedures used by Maddalena are shown in table 1.

Port A Cath
After implant assess pain and bleeding from the wound
After 24 h medicate with chlorhexidine 2%, and afterwards:
-score 1 (no redness, no pain): medicate every 7 days with transparent polyurethane
-score 2 (redness, no pain): medicate every 72 hours, with transparent polyurethane
-score 3 (redness, pain): medicate every 48 hours with sterile gauze, notify doctor
-score 4 (redness, soreness, pus): medicate every 24 hours with sterile gauze, notify doctor
-score 5 (bleeding): medicate every 24 hours with sterile gauze, notify doctor

Inspect and palpate every 24 hours to insert the Huber needle and document
For infusions, replace Huber needle every 7 days or in case of malfunction
After Huber needle removal, leave dressing for a couple of hours.

CVC
After 24 hours, medicate with 2% chlorhexidine and sterile gauze and transparent patch. Then after a week and every 72 hours afterwards:
-score 1 (no redness, no pain): medicate every 7 days with transparent polyurethane
-score 2 (redness, no pain): medicate every 72 hours with transparent polyurethane
-score 3 (redness, pain): medicate every 48 hours with sterile gauze, notify doctor
-score 4 (redness, soreness, pus): medicate every 24 hours with sterile gauze, notify doctor
-score 5 (bleeding): medicate with every 24 hours sterile gauze, notify doctor

Inspect and tap the insertion site and document every 24 hours.

PICC
After 24 hours, medicate with 2% chlorhexidine and sterile gauze and transparent patch. Afterwards:
-score 1 (no redness, no pain): medicate every 7 days with transparent polyurethane
-score 2 (redness, no pain): medicate every 72 hours, with transparent polyurethane
-score 3 (redness, pain): medicate every 48 hours with sterile gauze, notify doctor
-score 4 (redness, soreness, pus): medicate every 24 hours with sterile gauze, notify doctor
-score 5 (bleeding): medicate every 24 hours with sterile gauze, notify doctor

Inspect and tap the insertion site and document every 24 hours

Table 1. Nursing procedures used by Maddalena for the treatment of port a cath, PICC, and CVC

Venous thrombosis is a relatively common complication after placement of a venous access. The incidence is 1.7 per 1000/days with a catheter. The risk factors are cancer, a history of thrombosis, the site, and the type of catheter. Prophylaxis with anticoagulants is not useful. Ultrasound allows diagnosis of the presence and extension of thrombosis (2). The treatment involves the use of anticoagulants, while the removal of the catheter is reserved only for cases refractory to therapy or if anticoagulation is contraindicated. Thrombolytic therapy is indicated only for patients with serious and diffuse thrombosis who are not responsive to treatment. Anticoagulation should be continued for at least 3 months after catheter insertion (3). There is little evidence to recommend a type of CVC or a puncture site. Recommendations based on evidence have been extrapolated (4). Femoral catheterization should be contraindicated, or if not, as a last resort to gaining a venous site for a few days. The use of catheters impregnated with antiseptics or heparin is recommended to decrease the risk of infection for short-term CVC. The preventive use of antibiotics is not supported by scientific evidence. In the case of positive cultures, antibiotic treatment can be initiated. If not, in case of serious infections, the catheter can be left in situ and used for antibiotic therapy. Washing with heparinized solutions is recommended. Preventive use of dicumarolics or heparin is not recommended, although the use of a plasminogen activator is recommended to regain catheter patency after thrombosis. The removal of the catheter is recommended when it is no longer used or if a thrombosis that worsens despite anticoagulant therapy is confirmed.

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CHAPTER TWENTY-THREE L

SEXUALITY DISORDERS

According to the WHO, sexuality is a central aspect of life, concerning sexual identity and orientation, eroticism, pleasure, intimacy, and reproduction (1). Sexuality is a multidimensional concept, expressed by many personal, physical, psychological, cultural, religious, relational, environmental, and gender aspects (2). For these reasons it is difficult to consider a level of normality of sexual function. Sexuality is also defined as a process of giving and receiving pleasure and is associated with a sense of belonging and acceptance by the partner (3). Intimacy has been described as sharing of identity, closeness, and reciprocity connected to aspects of communication rather than sexual function (4). Sexual function is an aspect of life that is poorly considered compared to treatments and protocols during illness and in advanced stages when symptom control becomes a priority (5). Doctors often underestimate the problem, preferring to focus on cancer treatments and survival (4). These attitudes and a lack of knowledge of the alterations of sexuality represent a barrier to open communication on sexuality. Patients, on the other hand, are greedy for information, requiring support, help, and advice to settle doubts and assist them in living their sexuality in relation to the obligations that are related to illness and treatment (2). Sexuality tends to decline after a cancer diagnosis and does not improve afterwards. Cancer and subsequent treatments have a major impact on sexuality and intimacy, regardless of age, race, orientation, gender, or socioeconomic level (6). The causes of sexual dysfunction are of a physical nature, due to the treatment and progression of the disease, and of a psychological and socio-cultural nature (table 1).

- Reduced physical ability to give and receive pleasure
- Negative thoughts on one's body image
- Feelings of fear, sadness, depression
- Change of roles and relationships

Table 1. Causes of diminished sexuality in cancer patients.

Cancer and treatments can cause a dysfunction of what is considered normal individual sexuality. 50% of patients with breast or gynecological cancer and 70% of patients with prostate cancer have significant and lasting sexual dysfunction. The causes are generally of a physical and psychological nature. The most significant problems in cancer patients is the loss of sexual desire, the inability to maintain an erection in males, and local pain in women. Men lose the ability to ejaculate and reach orgasm. Women lose genital sensitivity, often with painful mucosal symptoms, and have difficulty achieving orgasm. In other cases, while maintaining some capacity, orgasm is delayed or prevented by the use of drugs or anxiety. In patients without disease, sexual problems persist unresolved and interfere with the return to a normal life (2).

Causes of sexual dysfunction

The causes of physical sexuality disorders include loss of function as a result of treatments, fatigue, and pain. Surgery, chemotherapy, and radiation therapy have a significant impact on sexual dysfunction. Age, previous sexual ability and bladder function before surgery, the location and extent of the tumor, and the extent of the resection are predictors for the appearance of sexual dysfunction.

- Psychological causes

Antitumor treatments can cause physical changes that modify the perception of one's image and attraction. The stress of a cancer diagnosis and subsequent treatment can further aggravate pre-existing problems. Sexual inter-relationships can also be affected by the feeling of being rejected by a potential partner who becomes aware of the disease. The use of drugs often overlaps with physical problems. Cancer and treatments can change the bodily sensation of oneself, and compromise one's physical self-esteem, with the consequence of not feeling so attractive (table 2) (7). Some of these modifications, such as weight loss and alopecia, may be temporary, but others are definitive, especially in the advanced stages of the disease (8). The intense emotionality connected with the diagnosis inevitably compromises quality of life and the capacity of psychological reaction, resulting in depression (9). Loss of sexual desire and decreased pleasure are typically an expression of depression, more frequently observed in the cancer population. There is a sense of loss of independence and of interest in life, which obviously also includes the sexual sphere.

- Weight loss, use of corticosteroids - Chemo-radiotherapy hair loss - Surgical hammers - Alteration of appearance for head and neck tumors - Colostomies, urostomies - Mastectomy, hysterectomy - Penis and testicle surgery - Vaginal consequences, bladder surgery - Incontinence

Table 2. Factors that influence body image

Sociocultural aspects have a strong influence on the sexual sphere. Patients with low socio-economic levels who recover from disease often maintain levels of anxiety and guilt regarding previous sexual activities, as if they were the causes of the tumor, or because of the fear of infecting their partners with the disease. Patients may be afraid of being rejected by the partner who becomes aware of the disease or has any disbelief about cancer and the impossibility of the disease being passed on. Patients may feel tired and worried that sexual activities may be difficult to do. Fatigue can make people lose their interest in sex. Older age is already in itself a condition in which desire and sexual performance fade. Nevertheless, sex can still be considered important and the loss of abilities produces a strong psychological distress (10).

The state of sexuality pre-existing the disease is fundamental. For example, positive attitudes favor a better recovery after treatment.

-Effects of the disease and treatments

a) Surgery

Although any type of surgery can affect the sexual sphere, genital and breast tumors are the ones that most easily cause marked changes (11). Despite improved improved techniques to save organ function, women undergoing uterus, ovaries, bladder, and other abdominal or pelvic organs may experience pain and loss of sexual function (12). The removal of the lymph nodes can cause edema in the lower limbs (13). The radical nature of the intervention involves a greater commitment, probably due to damage to the autonomous system. After vaginal reconstruction, patients may experience unpleasant sensations and lose the ability to contract muscles during intercourse due to the breakdown of the innervation of the new vagina and nerve injuries (14). Mastectomy produces an alteration of

body image that limits excitement, especially in patients sensitive to mammary touch (15). Malignant cutaneous lesions in the mammary area strongly inhibit intimacy and sexual activity.

In men, radical prostatectomy is frequently followed by a limitation of erection abilities due to damage to the nerve structures that control erection. This frequent complication (up to 90%) begins immediately after surgery and persists for a long time in many cases. The intervention also limits the inflow to the penis (16). It has been debated whether conservative nerve sparing techniques are more effective than radiotherapy in preserving erectile function. In men where an erection is maintained, ejaculations are dry due to the passage of the sperm into the bladder. Patients will experience an orgasm, but worry about this. These alterations produce infertility. An abdominal-perineal resection can damage the nerves that control erection and ejaculation, despite nerve sparing techniques (17). Gonadal dysfunction is common in patients with testicular cancer who undergo orchiectomy, particularly with the co-administration of chemotherapy (18). If both testicles are removed, the man will be infertile and probably incapable of having an erection. Incontinence has a devastating impact on sexuality. It represents the loss of control and of personal dignity. When a stoma is created, there is a great probability of alteration of blood supply to the genitals. Stoma can make a relationship problematic. With the removal of the lymph nodes, edema is observed in the tributary area due to the outflow obstacle. The impact of cancer of the head and neck tumors is devastating in relation to one's image and sexuality, even after reconstruction (19).

b) Effects of chemotherapy

Chemotherapy is frequently associated with loss of desire and decreased relationships. Side effects, such as nausea and vomiting, diarrhea, constipation, mucositis, weight loss, alopecia, and the presence of vascular access, make the patient feel less attractive. Generally these effects are temporary. In women, chemotherapy can modify the hormonal structure, modifying the cycle and mimicking an early menopause, with a symptom profile characterized by hot flush, irritability, sleep disorders, and vaginal dryness (20). Young women with breast cancer undergoing ovarian removal may present a similar picture. These patients develop sexual problems because of the fear that a replacement therapy can promote a recovery of breast cancer. Women undergoing bone marrow transplantation who develop a graft-versus-host disease may develop skin scars and vaginal tightening that limit relationships (21). Vaginal fungal infections are frequent in patients undergoing chemotherapy, receiving

corticosteroids or cycles of antibiotics, or with an immunosuppressive situation. Men may find difficulties during the treatment due to fatigue. Usually, this phenomenon is reversible. Chemotherapy can interfere with testosterone levels, which tend to come back online over time (22). Loss of desire and erectile dysfunction are quite common after bone marrow transplantation due to graft-versus-host disease or nerve damage (23).

c) Hormonal therapies.

Some substances are aimed at modifying the hormonal profile for disease control. Tamoxifen and anastrozole are widely used drugs in breast cancer (20). These substances have minor side effects, but they induce symptoms similar to those seen in menopause. Although ovarian hormones have an important function in sexual life, their use may not be sufficient to restore the alterations of sexuality and desire (24).

Men with testicular cancer remission have high values of gonadotropins and low testosterone values, with a negative overall impact on quality of life. Treatments that reduce testosterone values change the sexual sphere by reducing libido and erectile capacity (25). In some patients swelling of the mammary glands is observed which gives a feeling of reduced masculinity (26).

d) Effects of radiotherapy

Radiation therapy can also produce persistent effects, such as fatigue, nausea, diarrhea, and other symptoms that can interfere with sexuality. Pelvic radiotherapy can cause infertility in both sexes. In women, radiotherapy carried out for cancer of the rectum, bladder, or uterus, involves the ovaries and reduces the formation of female hormones (27). The production decreases slowly and causes the appearance of a postmenopausal syndrome. The risk of osteoporosis increases in the long term. Pelvic radiotherapy can cause vaginal damage, from an irritation phase to a fibrotic phase, resulting in narrowing and inelasticity, commonly associated with painful intercourse. Radiotherapy can also cause skin lesions in other locations (28).

In humans, pelvic radiotherapy for prostate, rectum, and bladder cancers produces damage on the sexual sphere with consequent reduction of erectile activity and fertility. The effect is gradual and develops within a few years (29). Probable causes are attributed to nerve injury, reduced arterial flow, or decreased testosterone (2). Brachytherapy preserves erectile and ejaculatory function better than radiotherapy and hormone therapy (30). In individuals with preserved ejaculation a dry sperm can be observed and ejaculation may be painful due to urethral irritation.

e) Opioids

Prolonged exposure to opioids may induce hypogonadism and consequent sexual dysfunction. In long-survivors opioids may produce signs of hypogonadism with high levels of depression, fatigue, and impotence. These effects are reversible with opioid discontinuation (31) (see chapter 19b).

Assessment

Sexual dysfunction is an unavoidable problem for patients with cancer in treatment or in the advanced stage (2, 32). However, there are many cultural barriers that limit an adequate assessment of sexual aspects and reducing the possibility of a therapeutic approach. These barriers are also present in the population undergoing palliative treatment, despite the best communication skills of the professionals (33). Professionals fear to be intrusive or feel embarrassed by ignorance, lack of time, or lack of confidence in intimate communication (34). The shelter environment poses further problems for limited privacy, while at home there is greater freedom of expression. Yet, patients are eager to talk about their problems and the impact of the disease on their sexuality that are hardly listened to (2).

Sexuality, and in any case intimacy, continues to be important even in the advanced stages of the disease, even if the emotional aspect prevails over the physical aspect (32). Sexuality should therefore be the prerogative of an overall evaluation. If sexual function is a relevant factor for quality of life, this aspect should be investigated. Unfortunately, doctors are not prepared or are reluctant to explore the intimacy of people.

A first step is gaining knowledge of the basic conditions. The clinical history and in particular the diseases that may affect sexual function, and aspects of lifestyle, such as the consumption of drugs, alcohol, and smoking, are well known risk factors for sexual dysfunction. Finally, a questionnaire to identify the presence of sexual problems can facilitate the emergence of a problem. Identifying the problem requires a more specific interview with the patient and the partner. An assessment should include the physical, psychological, and social aspects of cancer patients or long-survivors (35). The previous conditions should be known in order to quantify the changes reported by the patient and should concern the frequency of sexual desire, the capacity for erection or vaginal lubrication, and whether the embrace brings pleasure. Some ritual information is fundamental in evaluation: what means recur to facilitate erection or orgasm; what impediments there are to the relationship, like pain, and in

what way it is induced, when it is intense, and how long lasting it is; how long it has been since the diagnosis and treatment of cancer; what drugs have and are being used.

Another level of assessment concerns the psychosocial aspects, for example the personal meaning of sexuality, and the existence and stability of a relationship with a partner. It may also be helpful to know the partner's reaction to the diagnosis of cancer and whether this may have affected the physical and emotional relationship. Therefore it is important that the partners discuss their problems, concerns, and fears about their relationship with a professional who understands and can explain (36). Many patients are fearful and anxious about first sexual performance after treatment and may hesitate to resume intimacy. The partner can also be embarrassed to start activities that could create physical problems. These aspects should be discussed with a doctor who has frank and informal communication skills, and can provide practical advice to get around the difficulties of the first experiences.

From the purely clinical point of view, it is important to investigate some pre-existing diseases that can affect the sexual sphere. Some elements of lifestyle, such as smoking, alcoholism, or the use of various substances or drugs, can alter sexual function. Finally, some biochemical investigations, such as measurement of hormone levels, can provide useful information.

Treatment

A good communication of the existing situation, of the future possibilities, and of the possible remedies is fundamental (37). The partner should be an active and collaborating party. An active intervention on a spoiled pre-existing lifestyle and regular physical activity can improve mood, and probably even sexual skills can help.

Some patients may require medical intervention such as hormone replacement, the use of facilitators, or surgery. There is a variety of modalities available for patients with sexual dysfunction after cancer diagnosis and treatment. Patients can adapt to the new conditions by reading informative material and with the help of specialized personnel (38).

Some patients may be treated with hormone replacement therapy, medication, or surgery, as appropriate (39). For men there are means such as the Vacuum Constrictive Device, which is a penile pump. Filling produces a blood booster and an erection. Rings at the base of the penis allow the maintenance of an erection. There are numerous penile

prostheses, generally inflatable. Many drugs are now available to facilitate an erection, such as Viagra, Cialis, and Levitra. Prostaglandins E1 can be injected into the penis or administered ureterally to increase flow and induce erection. Each treatment has advantages and disadvantages in the individual case, especially for the psychological repercussions. Patients with more serious problems may require more intense psychological support on an individual basis. Couple interviews with an expert can be useful on how to deal with individual situations (40). The optimization of the depressive state and anxiety is a prerequisite for the effectiveness of each treatment.

In women, vaginal pain treatment is imperative. In addition, an expert can provide practical suggestions on how to improve intimacy, such as the use of lubricants or other material before and during intercourse to facilitate excitement and avoid vaginal pain. Estrogen therapy improves vaginal tone and elasticity, increasing flow and lubrication. The risks are variable according to the estrogen used. Flibanserin is an antidepressant that is used to treat loss of desire in premenopausal women, but it is not without side effects. There are alternatives to procreation that can be discussed before subjecting patients to treatments at risk of infertility (38).

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CHAPTER TWENTY-FOUR

RESPIRATORY SYMPTOMS

CHAPTER TWENTY-FOUR A

DYSPNEA

Dyspnea is a fairly frequent symptom in the cancer patient, with a prevalence varying according to the stage of disease of 20-90%, not necessarily linked to the presence of an organ pathology, a pulmonary tumor, or a cardiovascular disease. Dyspnea is considered an unpleasant subjective experience of a respiratory disorder characterized by distinct qualitative sensations of varying intensity, for the important psychological, social, and existential implications, all of which can amplify this symptom that strongly interferes with the quality of life (1). Dyspnea is also one of the most important expressions of distress at the end of life, due to its refractoriness to conventional therapies, and is one of the most frequent indications of terminal sedation.

Pathophysiology

There are some areas studied with imaging implicated in the activation of dyspnea, such as the anterior insular cortex, the amygdala in the limbic system, and the anterior cingulate tract, areas dense of structures typically used for affective modulation. As observed with pain, therefore, the perception of dyspnea depends on emotional and psychological components. The respiratory center located in the bridge of the brain stem coordinates the activity of the respiratory muscles, the diaphragm, the intercostal muscles, and the accessory muscles. It seems connected to other areas such as the cortex, which in fact voluntarily regulates the respiratory activity, as well as insula.

The respiratory center receives information on lung expansion and contractile force from muscular mechanoreceptors. A muscular effort against a given resistance (chronic obstructive bronchopathy) or in the presence of low muscular strength (neurological diseases or advanced stage of the disease) produces an unpleasant sensation of effort probably due to an increase not satisfied with the stimulation by the mechanoreceptors, but also by the increase of the efferent stimuli necessary to activate the respiratory muscles, which simultaneously activate the cortex, producing the typical sensation. There are also vagal afferents from pulmonary stretching

receptors, from receptors sensitive to chemical-physical irritants (broncho-constriction), and from receptors sensitive to interstitial and vascular pressure variations (pulmonary edema). Moreover, there are receptors sensitive to biochemical changes, such as partial pressure of oxygen and carbon dioxide. The medullary chemoreceptors are mainly affected by changes in pressure of carbon dioxide, while the carotid and aortic receptors are affected by changes in oxygen pressure. The most dyspneic effect is related to hypercapnia, while hypoxia plays a less significant role. There are adaptation phenomena, in chronic diseases in particular, which modulate the activation of these pathways, so that even high levels of hypercapnia or hypoxia are tolerated without apparent subjective sensations (1).

It is believed that the main mechanism resides in a disproportionality between the need to satisfy a respiratory effort (induced by afferent stimuli) and the inability to satisfy this need (efferent stimuli). If it is true that there is a multitude of mechanisms, independent or additive, with which the sensation of dyspnea can be produced. In chronic progressive diseases in particular, there is an anatomical and physiological subversion of the muscular structures, with the onset of an early beginning of anaerobic metabolism at low intensity load, which requires an increasing effort felt by the patient as intense suffering, in the attempt to hyperventilate when working at their maximum ventilatory capacity (2). It has been postulated that some individual mechanisms can induce qualitatively different perceptions that are expressed in a specific language. Neurological diseases or a state of severe fatigue with consequent muscular weakness are associated with dyspnea in the absence of a pulmonary disease, particularly in the last weeks of life. The main causes of dyspnea are listed in table 1.

Lung infections
Anemia
Chronic bronchopathy and respiratory failure
Bronchospasm
Pleural effusion
Pulmonary embolism
Muscle weakness
Carcinomatous lymphangitis
Pericardial effusion
Heart failure
Ascites

Table 1. Principal causes of dyspnea

Assessment

The sensation of dyspnea is strongly dominated by subjectivity. Some objective measures, such as gas analysis or respiratory rate, although useful for identifying the cause, cannot measure dyspnea. The one-dimensional numerical scale from 0 to 10, included in the ESAS (Edmonton symptom assessment scale) is easy to use for the obvious similarities with pain. Multidimensional scales (multidimensional dyspnea profile, MDP) (3) have also been used, which, in addition to the numerical scale, include the unpleasantness of sensation, the qualities of sensation (stress, hunger, mental effort, the sensation of closure of the respiratory tract, the need to breathe) and emotional response (depression, anxiety, frustration, anger, fear). Finally, the patient is invited to quantify the sensation as the volume of the sound emitted, beyond the feeling of unpleasantness.

In recent years, as observed for pain, the evaluation of dyspnea has been better conceptualized, as a function of exacerbation of the phenomenon compared to a sufficiently acceptable basic situation. Breakthrough dyspnea (episodic breathlessness) has long been included in the description of the phenomenon (4). Actually, in clinical practice there are peak intensities induced by an increased demand, as for example for an additional physical effort, although it is not excluded that emotional or psychological factors may also come into play, according to the mechanisms described (5). Onset and duration are even shorter than for breakthrough pain (6). Potentially, as in the case of breakthrough pain, a symptomatic medication could be used as needed.

Treatment

The treatment should be diversified in relation to the stage of the disease (figure 1). While causal treatment is necessarily the first choice when there is a good chance of reversing a challenging respiratory picture capable of ending dyspnea (lung infections, heart failure, pleural effusion), in most cases, especially in the advanced stage of disease, when the symptom no longer finds relief by the causal therapy, symptomatic treatment will be required. Beyond the presence of advanced cardiorespiratory pathologies, dyspnea will often be the end result of an extreme state of exhaustion, typically present in the last days of life (figure 1). The treatment of refractory dyspnea in the context of palliative sedation will be discussed in the appropriate chapter (see chapter 26).

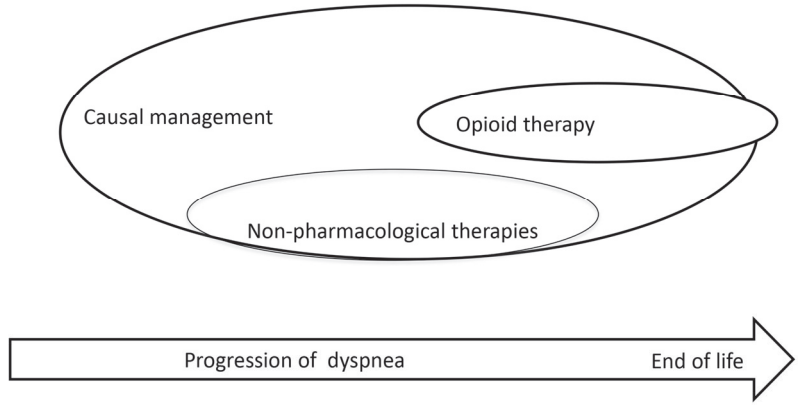

Figure 1. Progression of dyspnea along the course of disease.
Causal treatment: corticosteroids, antibiotics, anticholinergics, β2 agonists, O2, phosphodiesterase inhibitors
Non pharmacological therapies: respiratory and postural exercises

In chronic respiratory diseases, a treatment has been proposed according to sequential steps (7). As conventional therapies and non-pharmacological treatments lose their effectiveness, it will be necessary to intervene with symptomatic drugs, thus shifting the interest towards the use of opioids. Conventional therapies frequently require the use of drugs administered by inhalation, generally a β-agonist and anticholinergics. Corticosteroids are also often used or added. Systemically, theophylline preparations that are phosphodiesterase inhibitors are often used for the anti-inflammatory and oxidative anti-stress action. Corticosteroids, despite the absence of solid data, continue to be used for their anti-inflammatory properties.

Given the specific temporal pattern of breakthrough dyspnea, requiring rapid intervention, short-onset opioids could provide a clinical effect overlapping the onset and duration of an episode, resembling what has been largely reported for breakthrough pain. Although data are still insufficient to suggest specific recommendations, strategies such as avoiding exertion, pacing or using devices, or keeping calm have been described. Few controlled studies have investigated the effects of different formulations of opioids. Some data were gathered from studies assessing the pre-emptive use of rapid onset opioids, such as transmucosal preparations of fentanyl, followed by a provocative test, while other studies attempted to reproduce real-life conditions, given as needed. All

these trials were insufficiently powered to address the efficacy of fentanyl products over oral morphine or placebo, reflecting the difficulties in patient recruitment and the finalization of the studies. Strategies to prevent the occurrence of this phenomenon should be taken into consideration, including the optimization of the condition of persistent dyspnea or treating psychologic or environmental causes.

Non-pharmacological therapies include respiratory rehabilitation programs, with a particular emphasis on values, emotions, hopes, and fears. Pulmonary rehabilitation is proposed to reduce dyspnea by optimizing the patient's functional state and tolerance to exercise, and should be performed at an early stage, while losing importance in the more advanced stages of the disease when the patient's collaboration tends to decrease for obvious reasons (table 2).

Expiration with closed lips to produce positive expiratory pressure
Use of the diaphragm
Use of means to reduce the physical load
Use of small fans on the face
Posture facilitators
Relaxation therapies
Education for the patient and family members on the causes of dyspnea
Education on how to use drugs as needed

Table 2. Examples of non-pharmacological interventions

Opioids. Opioids are the drugs of choice for the symptomatic treatment of dyspnea. The physiological activity of endogenous opioids, which is inhibited by naloxone, on the sensation of dyspnea induced by exercise is well known. Opioid receptors are also well represented peripherally. In particular, they are present not only in the insula, a reception center for peripheral stimuli, where opioids would increase the time of apnea, but also in the respiratory tract, especially in the alveoli. Therefore opioids have a well-explainable positive modulatory function on these centers.

Experimental dyspnea induced by hypercapnia favored by the use of a breathing circuit is reduced by the administration of intravenous morphine (8). In many clinical and meta-analytical studies (9), opioids have demonstrated their efficacy in many clinical conditions associated with dyspnea. While no mortality has ever been observed, side effects are quite frequent, probably because fixed doses were used that did not take into account the level of dyspnea nor probably the level of opioid tolerance. Despite the potential of the inhalation route, opioids administered via this

route were not particularly effective. The administration of immediate release morphine in minimal doses for naive, even elderly patients resulted in a symptom control for about 4 hours, equivalent to its duration of action (10). Slow release morphine is also effective (11, 12). In clinical practice, however, patients receiving high doses of opioids for background control of pain do not suffer significant effects from low doses administered in naive patients without pain. As for the case of the treatment of breakthrough pain, also in this case the doses should be proportional to the dosage of opioids used for pain, since the patients are just tolerant. Furthermore, it is essential to distinguish the background dyspnea from the peaks related to the activity or to the triggers identified in each individual subject. The doses may be increased depending on the desired effect when tolerated by the patient. While the background dyspnea can be treated, generally with higher doses than those necessary to control the pain, such peaks can be treated as needed with opioids in doses proportional to basal opioid regimen, reminding in some ways of the treatment of breakthrough pain. Transmucosal opioids are gaining positions in this context, even if they are still in a preliminary study phase. The rapid onset and the short duration are potentially interesting requirements in breakthrough dyspnea.

Generally for doses of oral morphine equivalents of 60 mg/day, transmucosal fentanyl can be used at the lowest doses (for example, according to similar systemic availability, fentanyl buccal tablet, sublingual fentanyl, and fentanyl nasal pectin 100 μg), and higher dosages in a manner proportional in patients receiving higher doses of morphine. Table 3 shows some examples. Fear of respiratory depression is to be minimized because dyspnea, like pain, is notoriously a physiological antagonist of respiratory depression. Therefore, unless there are clear dosage mistakes in relation to the clinical situation, it is an improbable eventuality. Naturally, careful monitoring is necessary, especially in the early days, and in patients with an insufficiency of the excretory organs. Often the parenteral route is preferred, particularly in patients at the end of life, when collaboration is unlikely. Conversion requires a dose reduction to 1/3 of the dose calculated for the oral route (see chapters 16 and 17).

	Regular oral opioids for persistent dyspnea	Oral opioids BTP for episodic dyspnea	Fentanyl preparations for episodic dyspnea
Naive patient	2.5 mg x 6	2.5 mg	100 μg
Tolerant patient at 60 mg / da	12 mg x 6	12 mg	100-200 μg
Tolerant patient at 120 mg / day	25 mg x 6	25 mg	200-300 μg

Table 3. Initial approximate doses of opioids expressed in equivalent doses of morphine and fentanyl preparations of fentanyl of similar availability (buccal tablet, sublingual fentanyl, pectin nasal fentanyl), suggested for persistent dyspnea and episodic dyspnea, according to the level of opioid tolerance.

Sedatives - There is a mechanistic rationale for the use of benzodiazepines, possibly active on some areas involved in the perception of dyspnea. However, the scientific data are not entirely favorable, especially in patients with chronic respiratory failure (4), whereas the combination with opioids has been found to be useful (13). While they are irrelevant to dyspnea, they may be helpful in alleviating the expression of the symptom for the coexistence of anxiety or panic in periods of exacerbation. Chlorpromazine appears to have a certain efficacy, promotes nocturnal sleep, and is able to reinforce the effect of opioids, particularly in patients with confusional states.

Other agents - Local anesthetics are able to determine a reduction in bronchial reflexes, probably inhibiting vagal afferents. Occasionally, they can be effective, even if there is no evidence of their use. Furosemide, resulting in pulmonary decongestion, is quite effective, even if there are no specific studies except by inhalation. The use of corticosteroids is quite complex. Their anti-inflammatory function can improve dyspnea, for example in lymphangitis or in some acute phases. Although they are not recommended chronically in chronic respiratory diseases, their use is widespread and in some ways justified. Naturally, their use must be modulated during the different phases of the disease.

Oxygen - Oxygen is often given to the patient with dyspnea as a first measure, even in non-hypoxic patients. The use of oxygen in patients with hypercarbia, in which the only chemoreceptor stimulus is represented by hypoxia, can be dangerous. In most studies in the more properly palliative setting in particularly advanced patients, it was observed that air would have the same effect, beyond the determined oxygen pressure variations

(11). Similar results have been reported in a mixed population of non-cancer with chronic respiratory disease and cancer patients (14). It is therefore probable that the effect determines a healthy effect due to its symbolic meaning and a placebo effect. Already a flow of fresh gas on the face could have an effect, possibly due to the stimulation of trigeminal receptors (15). Oxygen or any fresh gas can therefore be useful and balanced with the decision of a clinically explicable suspension with the fact that the dyspnea does not always correspond to a determined oxygen deficiency, but this is often difficult to accept for family members.

Palliative ventilation

- ***Non-invasive ventilation (NIV)***

NIV includes both noninvasive positive pressure ventilation (NPPV) and continuous positive airway pressure (CPAP). During CPAP the flow and volume are generated by the patient who has a muscular activity sufficient to spontaneously breathe. In a strictly palliative setting, where the main goal is to manage severe respiratory distress in a patient near to death, CPAP alone does not theoretically have any role in relieving symptoms (with probably the exception of patients with end stage chronic heart failure), because it does not supply respiratory muscles as NPPV does. Unlike CPAP, during NPPV, the inspiratory flow is variably generated by the respiratory muscles and the pressure is partially or completely generated by the ventilator. NPPV is able to reduce dyspnea and improve oxygenation (16) and is often used as a substitute for tracheal intubation in the presence of an early declaration of a no resuscitation order (17).

In some cases NPPV allows the overcoming of a ventilatory crisis, potentially reversible, for the duration of a few days, as it may occur in hematologic patients. In some cases it may be useful for a preparatory intervention for family members who are not yet aware of the situation. The use of NPVV must then be weighed against the expectations of family members. Differently from traditional invasive mechanical ventilation, NPPV does not impair the patient's upper airway, and does not impair glottis function. NPPV is able to reduce the work of breathing and improve gas exchange while preserving the ability to cough, swallow, and speak. Furthermore, NPPV avoids iatrogenic complications associated with endotracheal intubation and reduces the risk of ventilator-associated pneumonia. In recent years, NPPV has been found to have a wide application not only in the intensive care setting, but also outside, and in home care. In patients with terminal disease, NPPV could be aimed at relieving dyspnea, similarly to pain, or could be used as a therapeutic

option to allow the saving of the time while gathering consent for diagnostic or therapeutic procedures, or simply while communicating the short prognosis when abruptly passing the patient from an intensive to a palliative care setting (18).

- ***High Flow Nasal Therapy (HFNT).***

Devices that deliver high flows of fully humidified inspired gas (up to 60 L/min) by dedicated nasal prongs are commonly named High Flow Nasal Therapy (HFNT) systems. The use of HFNT could be suitable as a first line therapy to relieve severe dyspnea. Recently, some studies have reported improvements in breathlessness using HFNT in many chronic diseases as well as in "do not to intubate" patients in intensive care. There are several mechanisms by which HFNT may reduce dyspnea and improve patient comfort (see table 1)

- Enhanced O2 pharyngeal concentration in patients undergoing oxygen therapy.
- Enhanced lung mucociliary clearance.
- Reduction in the metabolic expenditure of gas conditioning.
- Reduction in inspiratory resistance.
- Increased expiratory resistance
- Washout of nasopharyngeal dead space.

Table 4. Mechanisms of HFNT

- ***Clinical application of palliative ventilation***

NPPV might be an alternative option to relieve dyspnea in very advanced patients. Patients with end-stage cancer who are receiving only palliative care are potentially ideal candidates for NPPV, as most of them are patients with a "do-not-intubate" code. Some cancer patients have chronic pulmonary disease or cardiac disease and the occurrence of an acute exacerbation of these diseases, leading to acute respiratory failure, is relatively common. Most of these episodes may be promptly reversible, if adequately treated. However, these patients sometimes do not receive any form of ventilator support, just because they are labeled as cancer patients.

NPPV was used in a large group of advanced cancer patients in whom endotracheal intubation was questionable (19). The study included a series of advanced cancer patients with acute respiratory failure who had been judged by the referring oncologist to be suitable only for palliative care. The duration of NPPV was about 6 days. NPPV was feasible and useful in quickly improving some physiological variables, such as dyspnea, in end-

stage cancer patients with respiratory failure. The use of NPPV, while seeming to improve the immediate outcome in patients who were unlikely to receive any other form of ventilator support, did not produce any advantage on long-term survival. NPVV was more effective compared with oxygen in reducing dyspnea and decreasing the doses of morphine in patients with end-stage cancer (20). While NPVV can reverse hypoxemic respiratory distress, many patients have difficulties in tolerating a tight-fitting mask. Indeed, HFNT can provide comfortable delivery of high inspired FiO_2, giving a small amount of PEEP, especially keeping the mouth closed.

In advanced cancer patients with persistent dyspnea who were randomized to either HFNoxygen (HFNO) or BiPAP for two hours, HFNO was associated with improvements in dyspnea, although there were no significant differences between HFNO and BiPAP. Oxygen saturation improved with HFNO and respiratory rate decrease with both interventions. No significant adverse effects were observed. Thus, HFNT and BiPAP alleviated dyspnea, improved physiologic parameters, and were safe (21). There are various conditions that are more frequently afforded in the palliative care setting (see table 2)

- patients in the terminal phase of chronic respiratory disease who have already had NIV at home, and who have been given a “do not intubate/tracheostomize” order.
- patients with respiratory failure due to the disease or its complications, who have never previously received any ventilatory assistance but suffering from severe dyspnea not respondent to conventional therapy.
- patients who are temporarily treated with palliative ventilation, while waiting for further decisions and appropriate communication with family.

Table 5. Respiratory conditions more frequently afforded in the palliative care setting

For patients treated on long-term NPPV at home the main goal is to optimize their daily quality of life. Apart from facial skin breakdown, the real limitation to NPPV is sputum retention and mucus plugging. If the patient remains at home or is admitted to a palliative care unit, whatever the clinical situation, any unnecessary treatment should be withdrawn and the number of blood tests must also be restricted to the minimum. Particular care should be given to patients with amyotrophic lateral sclerosis, when the bulbar involvement may cause NPPV to be ineffective. In this case the ventilator should be adjusted to optimize the patient’s breathing and sedatives should be administered (22).

NPPV is aimed at decreasing dyspnea and optimizing patient's comfort. An essential pre-requisite before NIV is started in a palliative setting is to assess the benefits for the patient, as well as the skills and experience of the care-givers. NPPV settings should not cause patients discomfort and interface should be optimized to avoid leaks while fitting the mask to the patient. Oxygen should be targeted according to patient's dyspnea. Alarms should be turned off because they generate distress and may make family members even more anxious. The real priority is to make sure the patient is comfortable. Benzodiazepines, particularly midazolam, and opioid drugs can be administered if necessary to facilitate patients' compliance in the first hours until stabilization is achieved. NPPV may be uncomfortable and may cause undesirable side-effects such as skin lesions, irritation of the eyes, abdominal bloating, and, in rare cases, barotraumatic events. In addition, although NPPV is considered a "non-aggressive" technique, its use in a palliative care setting still remains debatable (23, 24). Thus, any palliative ventilation intervention needs to be discussed with patients, when possible, or relatives (see table 3).

- End-stage dyspnea should always be assessed regularly and as objectively as possible to "customize" the palliative treatment.
- Discuss with the patient and/or relatives the imminent problems and understand the patient's wishes concerning the appropriate choice when the time arises.
- Explain the goals of the patient's treatment in detail to the family/relatives assessing their understanding of the disease and its prognosis.
- Adapt communication according to the patient's and family's reactions.
- Stress that the treatment is designed to alleviate the symptoms and reassure the patient and family that the only goal is to make the patient as comfortable as possible.
- Discuss possible medical options (anxiolytics, sedatives, morphine) and non-medical options (oxygen, mechanical ventilation).

Table 6. Communication tasks when "palliative ventilation" is proposed

HFNT seems to offer some advantages, particularly for patient's compliance and acceptability, and should precede NIV application. Pioneer studies in palliative care patients near to end of life are limited and often of short duration. No information exists about the combination with common drugs used for relieving dyspnea such as opioids. Although palliative ventilation may be beneficial in short-term or long-term conditions, for example for respiratory failure in motor neuron disease, some patients may wish to stop the intervention or palliative ventilation may have exhausted his function. The withdrawal of any form of palliative ventilation appears to pose considerable challenges to palliative physicians for the emotional, practical, and ethical implications. Ethical and legal rights to withdrawal from treatment, discussions with family, discussions with colleagues, experiences of legal advice, and issues contributing to ethical complexity are the most challenging issues to address.

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CHAPTER TWENTY-FOUR B

COUGH

Cough, a very common symptom in the general population, is a particularly disruptive symptom in advanced disease, especially in lung tumors with infractions on the airways, with a prevalence of about 35% (1). Cough is a protective reflex that promotes the elimination of secretions. A chemical or mechanical stimulation stimulates the nerves present on the mucosa of the airways, of the transient receptor potential vanilloid-1 type, which transmit the impulses through vagal afferents to the medulla oblongata where there is a coordinating center of the reflex. A deep inhalation precedes the closure of the glottis and an increase in pressure. At the opening of the glottis, a turbulent flow of air is produced as a result of the accumulated pressure and thoracic muscular force, which remove the secretions from the mucous membranes, containing sufficient quantities of mucus. This reflex can be controlled centrally, even in terms of intensity. In some cases the cough, however, can be unproductive and may damage the mucosa. When a part of this reflex arc is missed, the effectiveness of the cough will be less (table 1).

Neuromuscular diseases
Weakness due to advanced disease
Decrease of the level of consciousness
Paralysis of vocal cords
Dryness of airways

Table 1. Causes of decreased cough reflex

Cough treatment is bidirectional, according to clinical intentions in relation to the need to increase its effectiveness or control the extent of the symptom. Treatment is initially causal, addressed to possible reversible factors, but in the advanced stages of the disease the symptomatic resources are rarely indicated. Antihistamines, bronchodilators, corticosteroids, antibiotics, proton pump inhibitors, anticancer treatments,

and endobronchial interventions are aimed at the identified local cause (table 2).

Lung tumors
Bronchial tumors
Pleural effusion
Chronic obstructive diseases
Infections
Use of ACE inhibitors
Esophageal reflux

Table 2. Causes of cough

In some cases protussive drugs, such as nebulized hypertonic saline and mucolytic agents can be used. Postural physiotherapy, assisted by appropriate insufflation machines, helps to eliminate secretions mechanically.

The suppression of cough involves the use of antitussive drugs, including opioids, which act on many stages of the reflex arc, especially the central ones. Codeine is very popular, although its effect is not confirmed by literature data (1). Its use in patients with sufficient opioid tolerance is questionable. Low-dose morphine showed good efficacy with a maximum benefit obtainable after a few days (2). Methadone is the most powerful antitussive drug, but requires some experience. Other opioids with low analgesic potency, such as dextromethorphan have invariably been used.

Sodium cromoglycate can reduce cough by its effect on the afferent intramucosal nerve fibers. Other drugs are available, although experiences in the cancer patient are limited. Local anesthetics, such as nebulized bupivacaine, provide some effectiveness in irritative forms.

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CHAPTER TWENTY-FOUR C

PLEURAL EFFUSION

Pleural effusion is a frequent complication in patients with advanced cancer either synchronously or with a disease recurrence. The pathogenesis is hematogenous, lymphatically, or by extension from adjacent organs. Lung, breast, and ovarian cancers account for 75% of cases (1). The presence of pleural effusion implies a negative prognosis ranging from 3 to 12 months (2). The main symptom is dyspnea, as well as cough. These symptoms strongly reduce the quality of life in the advanced stages of the disease (3). The diagnosis is performed radiologically and confirmed by a thoracentesis. The finding of exudative or hemorrhagic material is quite typical (4). A computed tomography can further provide information on possible pockets and on the spread of the primary disease.

Treatment

Apart from the treatment of the primary disease, it is necessary to relieve dyspnea with the removal of the liquid by the least invasive procedure possible in relation to survival expectations and performance status. The aspiration of the liquid may allow a temporary control of the breathlessness, but the reformation in the short term is very frequent and the re-performing of a thoracentesis multiplies the risk of complications such as pneumothorax, localization, or contamination. Therefore, thoracentesis should be reserved for patients with slow re-accumulation after the first thoracentesis, for tumors that respond to therapy, for patients with limited survival, or for patients who cannot tolerate invasive procedures such as pleurodesis (5). The insertion of a thoracostomy tube allows the draining of the pleural content continuously, connecting it to a water system. It can be inserted with a video-assisted technique that requires, however, pulmonary exclusion and general anesthesia.

Thoracostomy should not be kept long due to the risk of infections and pneumothorax. The reappearance of pleural fluid is observed in 80% of patients within a month from the removal of the tube. Therefore the

indication is for an expected short survival (1-3 months), while for other patients an alternative procedure should be considered (6).

After the pleural cavity has been drained, further formation should be prevented. Pleurodesis produces the obliteration of the pleural cavity through inflammation induced by chemical-mechanical substances until the subsequent fibrosis of the pleural sheets is obtained. A survival of more than 2-3 months should be considered to justify this intervention (7). Multi-use is ineffective in patients with a lung already trapped by disease or fibrotic processes (8). The most known sclerosing agents are certain chemotherapeutic agents, such as bleomycin or tetracyclines/doxycycline. With bleomycin a success is achieved in 60-80% of cases. Pain, fever, and nausea are frequently observed, and rarely there are more severe complications such as renal insufficiency and respiratory failure. Talc, less expensive, is the most used substance and is probably even more effective, although complications may be also observed with the use of this agent (9).

Traditionally, pleurodesis occurs with the placement of a pleural catheter after the removal of the greater amount of fluid. The tube is closed for 8 hours and then connected to an aspirator for 24 hours. Talc is sprayed also by videothoracoscopy under general anesthesia with a monopulmonary exclusion. The catheter is removed after 2 weeks. Povidone can be an alternative to talc for its low costs, and can easily be repeated. The pleurodesis is a palliative treatment and can only limit death by respiratory failure other than improving quality of life. Despite appropriate selection, 32% of patients do not survive 30 days later (10). It is recommended to use pleurodesis only in patients with pH >7.3 in the pleural fluid, for the correlation found between acidity and survival, and in patients with a good performance status (11).

- Thoracentesis. It is the only method for advanced patients with expected short survival. - Thoracostomy. Survival of at least one month. - Pleurodesis. Survival >2-3 months. Talc is the most effective, and the least expensive effective substance. For patients who can tolerate general anesthesia with lung exclusion, video-assisted thoracoscopy allows better vision as well as allowing a biopsy to be performed. For patients who cannot tolerate the technique, bedside placement is the best solution

Table 1. Indications in thoracentesis, thoracostomy, and pleurodesis.

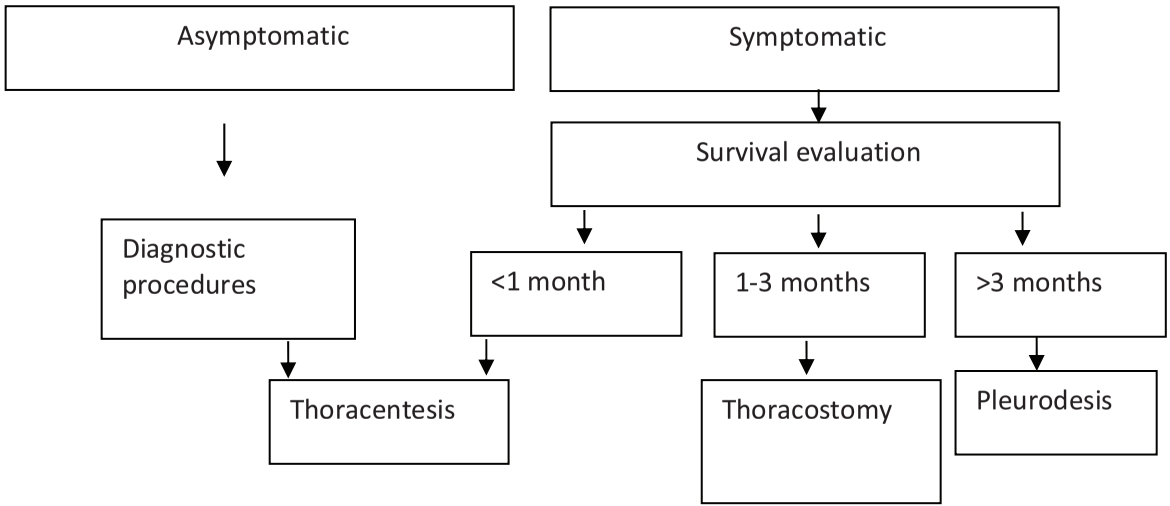

Table 2. Flow chart on treatments to be undertaken for pleural fluid removal

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CHAPTER TWENTY-FOUR D

HICCUP

Hiccup as a symptom of cancer or side effect of treatment is a rare problem (5%) but very challenging for patients because it produces insomnia, fatigue, and depression (1). It consists of a reflex arc represented by a vagal afference, the phrenic nerves, and the sympathetic chain, a not well known central site, and an efferent arm consisting of the motor fibers of the phrenic and intercostal nerves. Hepatic, diaphragmatic, and mediastinal disorders can induce the reflex arc by stimulating the vagal fibers. Some cerebrovascular diseases and Parkinson's disease are accompanied by hiccup. Finally, some drugs, such as corticosteroids and cisplatin, alcohol, hypocapnia, and metabolic and electrolyte abnormalities can induce this symptom. Often the cause is not identifiable and the treatment is based on few experiences. Low-dose gabapentinoids and, especially, baclofen, 5 mg three times a day, seem to be the most effective treatments. Alternatively, metoclopramide, haloperidol, chlorpromazine, and nifedipine have shown some effectiveness. Certain non-pharmacological strategies remain anecdotal (2).

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CHAPTER TWENTY-FOUR E

DEATH RATTLE

The respiratory secretions are produced along the tracheobronchial tree from mucosal cells under the control of the cholinergic system. These secretions are normally carried upwards through cough. When these secretions accumulate due to the lack of the cough reflex, they produce the typical noise similar to a bubbling of air, the rattle, corroborated by the presence of oropharyngeal secretions that are not swallowed (1). The lack of reflexes of cough and swallowing often recognize the same substrate, typically in the last hours-days of life: the extreme lack of muscular strength and a decrease in the state of consciousness, Patients with cerebral and pulmonary tumors seem to be more predisposed to the development of death rattle (2). This noise has a major impact on family members, as patients have often a low level of consciousness in these phases. Supporting family should be performed, providing useful explanation on patients' sensation. However, despite these attempts to normalize this phenomenon, the way a loved one dies leaves deep marks in the memories of the relatives and possibly it does not correspond to the concept of a peaceful death.

The treatment of death rattle is based on the use of anticholinergic drugs. However, it is evident that the presence of already formed secretions is difficult to reverse. This explains how in literature the effectiveness of anticholinergics is quite variable (3). Indeed, in patients with spontaneous or sedation-induced loss of consciousness, hyoscine buyilbromide should be administered as a pre-emptive measure to prevent secretions from forming everytime a low level of consciousness is developing, either spontaneously or with palliative sedation. An early administration of hyoscine butylbromide provided an effective method to prevent death rattle in most patients in comparison with the use of the same drug, once deatth rattle had been developed (4). The different modality of a timely administration of hyoscine butylbromide provided a relevant outcome, although some patients, estimated to be 40%, could receive a medication unnecessarily. Once formed, in selected environments the secretions can be gently aspirated with an appropriate

level of sedation and then a treatment with anticholinergics can be started (5).

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CHAPTER TWENTY-FIVE

EMERGENCIES

CHAPTER TWENTY-FIVE A

TUMORAL LYSIS

There are forms of more evident oncological interest such as tumoral lysis, spontaneous or due to antineoplastic treatment, which releases electrolytes and nucleic acids into the bloodstream that can determine important metabolic, cardiac, and renal effects due to hyperkalemia, hyperuricemia, and hyperphosphatemia.

Tumoral lysis is frequently observed in hematological diseases, but it has been documented in many other forms of cancer undergoing various treatments. It is characterized by the presence of at least two pathologic laboratory data regarding uric acid, potassium, and phosphates, that appear within four days of treatment. Increases of 25% or a 25% reduction for calcemia, and an increase in creatinine compared to the basal values, confirm the diagnosis (1). Clinically, it presents with oliguria, arrhythmias, and neurological symptoms, until convulsions.

Treatment

Treatment is consequential and aimed at correcting altered laboratory parameters. In some therapies in high-risk patients where cytotoxicity is expected, large hydration is suggested to maintain high diuresis, alkalizing with bicarbonate or acetazolamide to avoid urate crystallization (2). Allopurinol inhibits the oxidation of the xanthines, decreasing the production of uric acid, but is not able to alter the quantities of uric acid already produced. In this case rasburicase, an enzyme able to convert the formed uric acid, is suggested. This substance also avoids the accumulation of xanthines with consequent nephrotoxicity, which is instead observed with allopuridol (3). Hyperkalemia is treated with furosemide and the administration of glucose and insulin to promote cellular potassium re-entry. Ion exchange resins have a very slow action. Calcium gluconate can reverse electrocardiographic alterations and neurological symptoms related to hypocalcemia (4). Hyperphosphatemia is treated with the use of substances that incorporate phosphates, such as aluminum hydroxide, while in more severe cases, dialysis is indicated.

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CHAPTER TWENTY-FIVE B

ENDOCRANIC HYPERTENSION

Increased intracranial pressure secondary to a primitive or metastatic tumor results in devastating neurological damage. Therefore an immediate intervention is necessary. Most of the intracranial masses are metastatic, predominantly from a lung tumor (20%) (1). Survival without treatment is very short (about 4 weeks) (2). The prognosis depends on Karnofsky, on the extent of the disease, and on the primitive tumor (3). From the pathophysiological point of view, the hematological diffusion proportionally follows the areas with greater cerebral flow (4). The increased endocranial pressure is caused directly by the mass and by the cerebral edema as a consequence of a lesion of the blood-brain barrier, sustained by the local production of vascular-endothelial growth factor (5). The clinical presentation of brain metastases depends on the location, extent, and rapidity of tumor growth. In about half of patients the most frequent symptom is headache, generally described as tension which gets worse with maneuvers of increased thoracic pressure, and is often accompanied by nausea and vomiting, not necessarily present in the morning as traditionally described (2). Convulsions occur initially in 10-20% of cases and are caused by supratentorial lesions. Stroke occurs following emboli, bleeding, or arterial compressions. Hemorrhagic stroke is found most frequently in melanoma, thyroid cancer, kidney cancer, and choriocarcinoma (2). Cancer patients who report headache or changes in features, focal changes, or cognitive impairments should strongly suspect the appearance of brain metastases. The papillary edema will confirm the suspicion. The triad of hypertension, bradycardia, and irregular breathing is late and signals the danger of imminent death linked to herniation. Magnetic resonance imaging is the test that confirms the suspect and is able to differentiate the presence of a tumor mass from other brain lesions. Tomography is preferable when an acute event such as hemorrhage or hydrocephalus is suspected (6).

Treatment

Corticosteroids are the initial treatment of choice to reduce peritumoral edema and local cerebral compression through a reduction of impaired capillary permeability (2). Dexamethasone is usually used for its minor mineralocorticoid activity and the lower risk of infections and cognitive impairment compared to other drugs of the same class (see chapter 12). Dexamethasone seems to modulate the vascular growth factor and angiopoietin-1, and edema can be reduced by facilitating fluid drainage in the ventricular system (7). The doses should be 12-24 mg as a bolus initially, followed by maintenance doses of 4-8 mg every six hours (3). Mannitol can be associated in the most severe cases to decrease edema. Finally, mechanical ventilation with hypocapnia can reduce edema by limiting the cerebral flow. Mannitol and hyperventilation are transitory emergency and non-definitive treatments, to be reserved for critically ill patients with rapid neurological deterioration (8). The definitive treatment is represented by brain irradiation (WBRT), surgery, and stereotactic surgery. Irradiation increases survival by 3-6 months and is used in patients with multiple lesions or masses too extensive to be operable (5). The possibility of a surgical operation depends on the location of the mass. Removal is the fastest form of intracranial pressure control. Chemotherapy can be used in highly sensitive forms, such as germinomas, lymphomas, and pulmonary microcytomas. Seizures initially occur in 10-20% of patients with brain masses and are not necessarily associated with intracranial hypertension. An epileptic status requires urgent treatment, generally based on the administration of lorazepam or phenyntoin (6, 9). Patients with brain metastases who have never presented convulsions benefit from the preventive use of antiepileptics (10). The risk of bone marrow depression and possible interactions of phenintoine with other drugs that use the same metabolic system (see chapter 14) preclude the justification for preventive use (8).

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CHAPTER TWENTY-FIVE C

CARDIAC TAMPONADE

Pericardial effusion in the cancer patient is a consequence of a direct or metastatic involvement of the pericardium, generally by contiguity, as in the case of lung cancer, breast cancer, and mediastinal lymphoma (1), while mesothelioma is relatively less frequent (2). Antitumoral treatments, such as chest irradiation, may produce pericardial transudation and infectious pericarditis may develop in the presence of immunosuppression. The pericardial sheets form an elastic sac able to contain high volumes if the distension takes place slowly and gradually. The increase in pericardial pressure involves the cardiac chambers uniformly, but the right ventricular wall is thinner and most vulnerable to extrinsic compression. Flattening of the diastolic pressure between the cardiac chambers compromises the filling and conditions the cardiac output (3).

Pericarditis may be asymptomatic, even though its presence is associated with an unfavorable prognosis, especially if the effusion is greater than 350 ml. The development of a cardiac tamponade occurs with hypotension, jugular turgor, dyspnea, and precordial breath. The appearance of symptoms can also occur for smaller volumes if the formation of fluids is rapid. With a slow progression there will be a moment when the spill will cause a sudden drop in the cardiac output. Tachycardia is the most constant sign, and should be interpreted as a means of hemodynamic compensation (4). Radiographically, cardiomegaly is observed and ECG shows low voltages. Diagnosis is confirmed by ultrasounds, which demonstrate the right ventricular collapse in diastole and the conspicuous effusion.

Treatment

Ultrasound guided pericardiocentesis is the intervention indicated to quickly reverse the symptoms. A catheter can be left to dwell to avoid the accumulation of liquids (5). Adrenocarcinoma effusions tend to reform quickly and suggest to perform a pericardial window (6). Decompression

can produce hemodynamic effects of re-adaptation instability and may require intensive hemodynamic support. These phenomena are more likely observed in hematological diseases and after the removal of large volumes (7). Before carrying out intensive operations, survival expectation and risks associated with the procedure must be considered.

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CHAPTER TWENTY-FIVE D

SUPERIOR VENA CAVA SYNDROME

The superior vena cava drains the venous flow from the head, upper limbs, and upper chest. Primitive and metastatic tumors can compress the thin venous walls and prevent adequate venous return from tributary areas. The most strongly associated cancers which may produce this syndrome are those of the lung and breast, and lymphomas, thymomas, and germinomas. Among the non-cancer forms of caval compression, aortic aneurysm, mediastinal fibrosis, thyroid hypertrophy, granulomatosis, and thrombosis should be considered.

The severity of the caval compression depends on the speed with which it is formed. The syndrome can be limited by the formation of collateral circuits through the azygos veins and the internal mammary veins. Obvious signs appear in the form of edema in the upper limbs, facial and orbital edema, stridor, and dysphagia due to the narrowing of the airways and pharynx, up to the appearance of hypotension. Headache is a consequence of the distension of cerebral vessels of the dura and the formation of cerebral edema involving also the cognitive state. Tomography and magnetic resonance imaging can be used to verify the site and the extent of the obstruction (1).

Treatment

Vena cava syndrome requires fairly rapid intervention, although the presentation is usually progressive (2). Instead, patients with neurological disorders require immediate treatment. The placement of a venous prosthesis allows a rapid resolution of symptoms (3). Corticosteroids are often used, although efficacy is not documented (4). Biopsy determination may allow targeted chemotherapy treatment when the clinical presentation allows, in particular with pulmonary microcytomas, lymphomas, or germ cell tumors.

Mediastinal irradiation determines a rapid resolution of the symptoms in spite of the minimal luminal variations produced on the vena cava, probably because in the meantime it allows the formation of collateral

circulation. In the case of thrombosis by central catheter, the use of thrombolytics can resolve thrombosis, with fibrinolytic instillation. Anticoagulants or high-dose heparin are possible alternative treatments (see chapters 23k and 25e), even if they require longer times. Such treatments should be weighed up carefully in patients in whom brain metastases have not been excluded (5).

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CHAPTER TWENTY-FIVE E

COAGULATIVE DISORDERS AND EMORRHAGE

Cancer patients may present many conditions that cause bleeding, in the form of hemoptysis, hematuria, melena, hematemesis, or bleeding from cutaneous or vaginal lesions. In some cases these episodes represent a real clinical emergency. Hemoptysis is typically present in bronchial tumors and can be fatal (1). Vaginal bleeding is widely represented in endometrial tumors, although most do not take on dramatic tones. It is a consequence of tumor invasion that often includes the rectum and the bladder. Gastrointestinal bleeding may affect the upper tract, generally the stomach, and the lower tract. Hematuria is the consequence of a bladder lesion, a discoagulopathy, or pelvic irradiation. In some cases, hemorrhage, as in the case of rupture of a large vessel due to tumor infiltration, is the culminating moment that leads to death (2). The causes of hemorrhage, local or systemic, are shown in table 1.

- *Local*
Tumoral invasion of vessels
Bleeding tumor surfaces
Severe mucositis
- *Systemic*
Drugs (anticoagulants, anti-inflammatory, interactions)
Non-cancer hematological diseases
Thrombocythemia or alteration of platelet function
Medullary invasion
Intravascular coagulation
Hepatic insufficiency

Table 1. Causes of hemorrhage

Besides the local forms generally initiated by a tumor lesion, there are some systemic forms that can overlap the first ones. Disseminated intravascular coagulation is a systemic syndrome in which thrombosis

followed by bleeding is observed, characterized by a sequence of events: exposure to pro-coagulant substances, such as some tissue factors, fibrin formation, fibrinolytic response, factor consumption coagulation, and the consequent hemorrhage with involvement of the peripheral organs (figure 1). Therefore, in addition to bleeding, thromboembolism can also be observed at various levels. Petechiae and skin bleeding at the site of wounds or catheters visually reveal the syndrome, which can be fatal, especially in acute forms, often supported by hematological diseases.

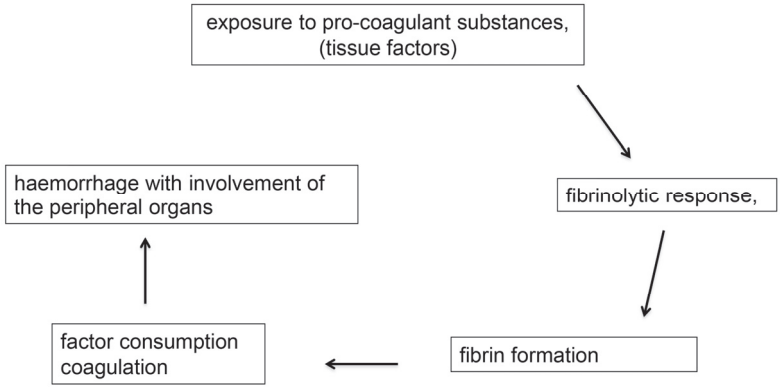

Figure 1. Disseminated intravascular coagulation

In chronic forms where events are more moderate and compensated, patients may be less symptomatic. Solid tumors are the most common cause. Thrombosis occurs both at a venous and arterial level. Clinical history, thrombocytopenia, fibrinogen decrease, and an increase in fibrin degradation products allow diagnosis. Minor forms may also not require intervention in some cases, especially acute forms with local bleeding. Hemodynamic support and the replacement of some plasma components (platelets, plasma) may be efficacious. Antifibrinolytic substances (aprotinin and aminocaproic acid) are contraindicated for possible thrombotic complications. The use of heparin is not supported. Thrombocytopenia, which is observed as a consequence of myelotoxic treatment, especially in hematological tumors, is associated with a high risk of cerebral hemorrhage. The threshold for spontaneous bleeding has been established to be 50000/μL. Paradoxically, the probability of bleeding has been found to decrease below values of 10000/μL. The indication for a platelet transfusion remains controversial and is generally indicated in the presence of bleeding or in anticipation of a procedure. The

risk of bleeding depends not only on the platelet count, but also on the underlying disease, on the use of other drugs that interfere with platelet function, and on other complications such as infection or coagulation deficiency (1).

Treatment

An accurate review of the history of the disease and of the current localizations, together with a clinical examination and laboratory investigations, may suggest the etiology of bleeding and the causal treatment. In advanced patients many other factors will need to be considered, such as the availability of resources, the setting, the burden of symptoms and quality of life, life expectancy, and, of course, the patient's will. The prospect of sudden and fatal bleeding requires intense psychological work. Therefore, the choice of a more or less intensive treatment must be balanced by a risk assessment in relation to the precariousness of the conditions (see chapters 2 and 3) (3). The treatment should be individualized, considering the scarce available evidence, and preceded by an assessment of the causes to undertake as specific a therapy as possible.

a) Local treatments

A first option is that of a local treatment to promote hemostasis for vaginal, rectal, or nasal bleeding, with a bandage and hemostatic substances, such as thromboplastin sponges, or topical administration of gelatin. Other bioabsorbable fibrin-based substances can be applied to hemorrhagic lesions. Finally, gauze soaked in vasoconstrictors can restrain capillary bleeding (for example nasal).

b)Interventional treatments

Radiotherapy and bronchial surgery, embolization, or the use of bronchial stents, and endocavitary laser therapy are the possible causal treatments for hemoptysis, if the general conditions allow it (4-6). Radiotherapy is also used for gynecological, bladder, and rectal bleeding, while in patients with head and neck tumors, it has generally been already performed and therefore would require a treatment at the same site (7). In gastrointestinal hemorrhages, in addition to radiotherapy, the most frequent treatment is endoscopic (thermocoagulation and local injections of vasoconstrictors). Embolization may be another weapon in cases where

there is vascular accessibility for the advancing of a catheter (8). Surgery is rarely used, typically in patients with head-neck tumors with imminent vascular rupture.

The presence of large bladder clots requires specific intervention with a multiple-channel catheter to irrigate the bladder. This procedure is painful and requires an analgoanesthesia. If bleeding is refractory to conservative treatment with instillations of aluminum sulphate, it can be tested with silver nitrate, even if there is a risk of renal failure or embolization. Another option is radiotherapy treatment and the use of tranexamic acid. Endoscopic laser-resection is indicated for the most resistant cases. Cystectomy and urinary surgical diversion is reserved only for patients with excellent performance (9).

c) Medical treatment

Antifibrinolytics inhibit the conversion of plasminogen, thus reducing fibrin lysis. They are the most commonly used drugs for bleeding. Other systemic interventions involve the use of vitamin K in conditions of the deficiency of some vitamino-dependent coagulation factors or to treat patients receiving warfarin. Vasopressin, a visceral vasoconstrictor, and somatostatin analogues, reduce portal pressure and may limit gastrointestinal bleeding. Endoscopy is used when previous hemodynamic substances have not worked, to block gastrointestinal bleeding with cauterization or the instillation of vasoconstrictors. Transfusion of blood products is very controversial. The indication for the use of platelets in hematological diseases is not dependent on the plasma values, but rather on the clinical condition (oral bleeding, epistaxis, hematomas).

In the advanced stages, the choice to use or not platelet transfusions poses ethical problems because it also corresponds to the decision to suspend the therapies. Therefore the communication of the futility of this intervention will have to be shared with the patient and/or their family members with effective communication (see chapter 3).

Plasma transfusions are indicated in the presence of deficiencies of some factors, in patients in whom it is necessary to reverse the effect of anticoagulants, in patients requiring urgent surgery, and in intravascular coagulation, while blood transfusions should be reserved for patients who present blood losses and are symptomatic (see chapter 23g) (1).

In the final phases of life, the approach should be directed to behaviors such as the application of pressure dressings on visible areas of bleeding and adequate psychological support. Even the use of dark tablecloths that can limit the visualization of blood can be helpful (10). Acute unrestrained

hemorrhage is an indication for a prompt sedation to alleviate distress in the last hours of life (see chapter 26).

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CHAPTER TWENTY-FIVE F

PULMONARY EMBOLISM

The risk of pulmonary embolism is relatively high in patients with advanced chronic diseases, particularly with malignancies. Most patients with cancer present coagulation abnormalities indicative of up-regulation of the coagulation cascade, increased platelet activation, and aggregation. Pulmonary embolism causes approximately 1-2% of cancer-related deaths, and about 5-10% of pulmonary emboli are considered life threatening. The mortality in untreated embolism is high (30%) but appropriate treatment may decrease it to 2-18%. Pulmonary embolism is a well-known poor prognostic factor in cancer patients, as the result of a direct relationship with fatality or an association with more aggressive tumor biology. The complex interactions between tumor cells and pro-coagulants have also been associated with the progression of cancer. The coagulation system, which is activated in most cancer patients, has an important role in tumor biology, as it may make a substantial contribution to tumor angiogenesis and metastasis (1).

Pulmonary embolism has its origin in other sites, including the legs or pelvis, where deep vein thrombosis is present. Clots can break off from a vein in the leg or pelvis, and travel through the circulatory system to end up in the pulmonary artery, blocking the supply of blood to the lungs. Many triggers can lead to the formation of a deep vein thrombosis/pulmonary embolism in cancer patients. Acute leukemia, glioblastoma, and kidney, lung, and pancreatic cancer are highly likely to cause thromboembolism. Moreover, several cancer treatments can lead to blood clots, such as chemotherapy or hormone therapy. An increased risk of developing this coagulative disorder is present during the postoperative period after surgery, as patients are immobile or have central venous catheters (1).

The main symptoms of a deep vein thrombosis are pain and swelling in the calf, behind the knee, and up into the thigh. The main symptoms of a pulmonary embolism are sudden shortness-of-breath and chest pain. Thus, the clinical presentation of pulmonary embolism is often nonspecific, as it includes shortness of breath, chest pain, fainting, hemoptysis and cough,

suggesting a respiratory infection, cancer progression, or a complication of chemotherapy and radiotherapy. A physical examination of the patient most often reveals tachycardia, tachypnea, and auscultatory changes over lung fields, as features of right heart failure-jugular vein congestion. The clinical picture and course of acute pulmonary embolism depend on the number and diameter of the choked arteries. Thus, manifestations range from a small asymptomatic to a life-threatening condition with subsequent hypotension and cardiogenic shock.

The diagnosis of PE may be hampered by the presence of lung metastases and lung injury secondary to radiotherapy and/or chemotherapy. The clinical symptoms and radiological features are unable to distinguish it from embolism caused by tumor material.

Diagnosis on the basis of the clinical picture alone is difficult. Clinical suspicion of this complication requires the inclusion of anticoagulant therapy with simultaneous diagnostics aimed at reaching the correct diagnosis.

Deep vein thromboses and pulmonary emboli are diagnosed by imaging exams, including ultrasound/Doppler study for a deep vein thrombosis, and CT angiography, chest radiography, and EKG for a pulmonary embolism. The D-dimer test in the diagnosis of thromboembolic events has been proven its efficacious in the diagnosing and monitoring of pulmonary embolism after treatment (3).

Treatment

Anticoagulation should be started in all patients in whom venous thromboembolism is a serious consideration. Options for acute management include adjusted-dose unfractionated heparin (UFH), fixed dose of low-molecular-weight heparins (LMWHs), or Fondaparinux. Fondaparinux is a synthetic drug with antithrombotic activity that results in selective inhibition of factor Xa mediated by the inhibition of antithrombin III (ATIII). The neutralization of factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effect on the platelets.

There are some options for chronic anticoagulation. When an oral vitamin K antagonist is chosen, a parenteral agent (e.g., UFH, etc.) is required for at least 5-7 days until an INR of 2-3. LMWHs significantly reduce the incidence of recurrent VTE when compared to oral vitamin K antagonists, with no differences in bleeding complications (4-7). Moreover, LMWHs simplify the treatment. Thus, LMWHs are preferable

to full dose warfarin for initial treatment of cancer-related VTE, particularly in the first 3-6 months. Anticoagulant therapy should be continued indefinitely or until the cancer has resolved, although the safety and efficacy of LMWHs in cancer patients beyond a treatment duration of 6 months is unknown.

Upper extremity DVTs secondary to central catheters respond well to anticoagulation without removal of the catheter (8). Anticoagulation should be continued for as long as the catheter is in place and for at least 3 months after its removal (9).

The recommendation is for a minimum of 3 months of therapy (10). Given the inherent risk of major and, rarely, fatal bleeding (11, 12) thrombolytic therapy should be restricted to life- or limb-threatening thrombotic events (10).

Vena cava filter insertion is commonly performed for recurrent pulmonary embolism, extension of deep venous thrombosis despite anticoagulation, and when anticoagulation is contraindicated. The use of cava-filters, however, is not associated with any mortality benefit (13, 14). Complications include filter thrombus, embolization, and fatal pulmonary embolism, as well as fracture, and migration of retrievable filters (15, 16). Thus these filters should be used in the setting of acute situations where a patient cannot receive anticoagulation.

Thrombolytic therapy for sub-massive pulmonary embolism failed to show any benefit on mortality (17), adding a risk for bleeding complications. Systemic thrombolytics should be reserved for massive pulmonary embolism.

Recurrent venous thromboembolism despite adequate anticoagulation is common among cancer patients (18, 19). Patients on treatment with oral vitamin K antagonists should be switched to LMWHs and those being managed with LMWHs should increase the dose by 25% (20). In unresponsive patients, a further dose escalation should be attempted (21).

Deep vein thrombosis	LMWH for acute and chronic therapy UFH, LMWH or Fondaparinux with transition over 5-7 days to warfarin (INR 2-3) is an acceptable alternative if LMWH not feasible Duration at least 3 months or for as long as cancer active (whichever is longer) For massive DVT, consider catheter-directed

	pharmacomechanical thrombolysis
	If anticoagulation contraindicated, consider retrievable vs. permanent vena cava filter
Pulmonary embolism	LMWH for acute and chronic therapy
	UFH, LMWH, or Fondaparinux with transition over 5-7 days to warfarin (INR 2-3) is an acceptable alternative if LMWH not feasible
	Duration at least 6 months or for as long as cancer active (whichever is longer)
	For massive PE, consider thrombolytic therapy
	If anticoagulation contraindicated, consider retrievable vs. permanent vena cava filter
CVC-related deep vein thrombosis	Initial therapy with UFH, LMWH, or Fondaparinux with transition over 5-7 days to warfarin (INR 2-3)
	Remove catheter if symptoms fail to improve or catheter no longer needed
	Duration at least 3 months or for as long as catheter is present (whichever is longer)
	For massive CVC-related DVT consider thrombolytic therapy
Superficial venous thrombosis	If distal, consider symptomatic therapy with compresses, NSAIDs and continued observation
	If proximal (above knee), consider LMWH with or without transition to warfarin (INR 2-3) particularly with clots within 2cm of deep venous system
	Duration of therapy 1-3 months

Table 1. Therapeutic recommendations for venous thromboembolism in cancer

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CHAPTER TWENTY-FIVE G

SPINAL CORD COMPRESSION

Spinal cord compression is defined as a displacement of the meningeal sac around the medulla by a mass. Compression may be a consequence of a posterior extension of a vertebral mass or an anterior extension of dorsal elements, or a bone growth which invades vertebral foramens. More rarely, metastases are directly medullary or meningeal. In most cases the metastatic spread is hematogenous with invasion of the epidural space. In 15% of cases, especially in neuroblastomas and lymphomas, it may be due to diffusion from adjacent tissues, such as the paravertebral masses that make their way into the spinal cord through the vertebral foramina. The most common site is thoracic (60%), followed by the lumbosacral site (30%). Often the levels are multiple (1).

Spinal cord compression is a neurological emergency to be considered seriously because the functional outcome of a treatment will be dependent on the timing of the diagnosis. It is in most cases due to vertebral and peridural metastases that invade the posterior peridural space rather than a direct medullary or leptomeningeal involvement. The presence of this mass produces edema and reduction of vascular supply to the spinal cord and to the roots. Breast, lung, and prostate cancers often affect the thoracic vertebrae, while pelvic tumors preferentially involve the lumbosacral sites. Myeloma and lymphoma are other cancers that can produce spinal cord compression. The existing studies have hardly taken into consideration the natural history of the disease (2). Some diagnostic factors are known, but their weight does not remain firmly established. While vertebral pain is too frequent in other conditions to be considered an absolute risk factor, some more direct elements have been identified (table 1):

- inability to walk - increase in tendon reflexes - radiological presence of compressive fractures - presence of bone metastases - bone metastases diagnosed a year earlier - age over 60 years.

Table 1. Diagnostic factors for spinal cord compression

In the absence of one of these signs the possibility of a spinal cord compression is minimal (3), while the presence of at least five of these factors leads to a diagnosis in almost 90% of patients. Pain is therefore not a discriminating factor because it is present in many other clinical conditions. The localization of pain at the cervical-thoracic level, the progressiveness, the pain being exacerbated by physical activity, cough, and abdominal efforts, which increase the pressure inside the spinal cord canal, are suggestive elements. Therefore, patients with vertebral metastases who experience progressively increasing pain should be carefully monitored. The progression towards definitive neurological damage is variable. Patients with long latency get the best results from decompression. The presence of radicular pain, difficulty in walking, muscle weakness, and sphincter changes increase the odds.

On the other hand, the absence of pain does not exclude a spinal cord compression. Therefore it is important to evaluate the temporal pattern of events. Clinically, the warning signs, often ambiguous, do not always receive the right attention. The first sign is back pain, which may also be mild initially but progressively becomes intense. Pain is referred to as a band around the thorax or abdomen and may radiate to the buttocks or lower limbs. Neurological signs will be different depending on the affected vertebral site. In cervico-thoracic lesions pain radiates to the upper limbs. Often the pain gets worse in the supine position, thus disturbing sleep. Paraesthesias in the feet and loss of strength are initial nuanced signals that progress with more defined frames until the loss of sensory and motor functions. A worsening vertebral pain, especially with movement or coughing, should suggest an immediate implementation of radiological investigations. There is a feeling of not being able to stand up well, and of having difficulty climbing stairs, walking, or simply moving the legs. A cauda equina syndrome will mainly produce sphincter disorders (4).

The presence of some suggestive elements (table 2) must immediately lead to the execution of diagnostic imaging studies. The standard

radiological examination does not always highlight a useful image, especially in cases of lymphoma, where only an integration with MRI can highlight the vertebral and extra vertebral extension of the compressive mass. Scintigraphy, which is not decisive for the diagnosis, can be useful for detecting any other bone metastases at a distance.

- Thoraco-cervical pain
- Worsening lumbar pain
- Pain induced by cough, extension, abdominal strain, acupressure, or nocturnally in the supine position
- Radicular pain with weakness in the lower limbs, difficulty walking
- Sensitivity deficit
- Sphincter dysfunction

Table 2. Alarms for an early diagnosis of spinal cord compression

A severity score of compression derived from MRI has been proposed (table 3) (5). Patients who develop vertebral metastases are at risk of irreversible neurological damage. Physical abilities pre-existing at diagnosis are determinants of the result after treatment, in terms of physical recovery, independence and therefore of quality of life, and survival.

Grade 0	Bone disease only
Grade 1	Initial peridural involvement without thecal deformation
Grade 1b	Thecal deformation without medullary involvement
Grade 1c	Thecal deformation pushing spinal cord but without compression
Grade 2	Spinal cord compression with fluids around the spinal cord
Grade 3	Spinal compression without fluids around the spinal cord

Table 3. Severity score for spinal cord compression, based on MRI

The severity of the medullary damage and the loss of sensory and motor functions were classified with a score (see table 4).

Grade	status	sensibility	motor dysfunction below the compression level
A	Paraplegia	no sensibility	complete paralysis
B	Only sensibility	partial	complete paralysis
C	Unable to walk	normal	minimum function, insufficient
D	Able to walk		partial function
E	No symptoms		normal

Table 4. Severity of spinal cord damage and function (Frankel classification)

Treatment

Patients with asymptomatic vertebral metastases are not routinely treated with radiotherapy or surgery. Timely treatment, when the patient is still walking or within 24 hours of the appearance of neurological deficits, translates into a more certain recovery. Even when the diagnosis is made later, decompression leads to functional improvement (6).

By contrast, an excessive delay produces complete and irreversible damage with consequent paralysis, loss of functional independence, and consequently limited survival. Therefore diagnosis requires immediate treatment to reduce the tumor mass and save the vascular and nervous structures. Treatment should take into account the patient's needs and preferences. Good communication about therapeutic opportunities in these circumstances is of paramount importance. Furthermore, it is essential for patients with known vertebral metastases to be warned not to underestimate any signs of this complication for a timely intervention. The appearance of chest pain, a progressively increasing pain in the lumbar region which is aggravated by maneuvers which bring about an increase of abdominal-thoracic pressure, with nocturnal pain and acupressure must alert the patient (table 2).

Patients with suspected vertebral instability should be treated with provisional alignment media pending further details. The choice of treatment depends on certain factors, such as the type of tumor and the area being offended. In the expectation of treatment, an orthopedic support can be provided to avoid dangerous loads on the column.

Corticosteroids are the most effective drugs to reduce edema and therefore pressure on the structures involved, and should be administered at high doses in the slightest suspicion of spinal cord compression. The

doses may be decreased over time until suspension after initiating a causal treatment. Corticosteroids, if not contraindicated as in the case of the presence of a lymphoma, should be given in medium to high doses (at least 16 mg/day) while waiting for a decision. It is important to know the histological aspect of the disease for a possible chemotherapeutic intervention, as well as a complete staging of the possible sites of disease and their extension, and the general conditions of the patient (table 5).

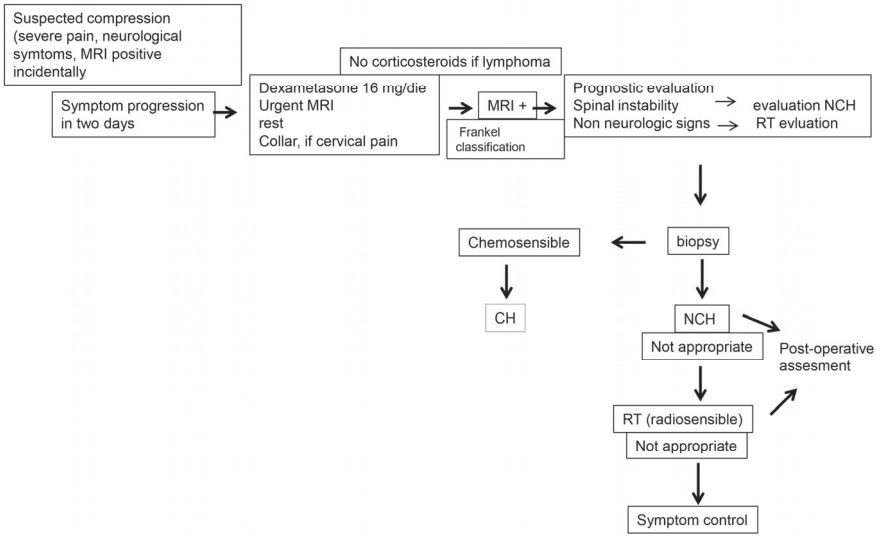

Table 5. Flow chart for the management of spinal compression. CH = chemotherapy, NCH = neurosurgery, RT = radiotherapy, MRI = Magnetic resonance imaging

Neurosurgery should be considered only if life expectancy is more than three months and in patients who have not yet suffered significant neurological damage to achieve functional recovery (7). Decompression alone is indicated only for isolated peridural tumors or metastases of the vertebral arch without instability. In all other cases decompression should be accompanied by internal fixation, possibly with vertebral reconstruction for those who have an expected survival of one year (8).

Radiation therapy should be the definitive treatment for patients with epidural masses, and without neurological damage, mechanical pain, or spinal instability. For patients with a short prognosis, a single fraction of 8 Gy should be preferred, while for patients with longer survival, 30 Gy can

be used in 10 fractions (9). Postoperative radiotherapy should be performed in all patients who achieve a good surgical result after the healing of the sutures. Radiotherapy is urgently required (within 24 hours) in patients who cannot be operated, unless patients are already paraplegic, pain is controlled, and the prognosis is short.

In the event of complete paralysis, the transition to palliative care is essential. For patients who remain bedridden appropriate measures should be introduced, with an anticoagulant treatment, and management of pressure ulcers (see chapter 23i). The function of the urinary tract should be ensured, possibly by placing a urinary catheter in a chronic or intermittent manner. Similarly, all the necessary care must be taken regarding intestinal transit, constipation, or incontinence, depending on the level of neurological damage. Respiratory physiotherapy is important, especially for thoracic vertebral lesions.

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CHAPTER TWENTY-FIVE H

METABOLIC EMERGENCIES

Hypercalcemia

This is a fairly frequent complication among the metabolic forms, frequently associated with tumors that tend to produce bone metastases (1). Various mechanisms may underlie the increase in calcium values: the release of a peptide similar to parathormone, which does not require the presence of bone disease, the paracrine stimulation of osteoclasts, which produces osteolytic effects, or the release of vitamin D-like substances from the tumor (2). In most cases hypercalcemia is a consequence of the release of the parathyroid hormone peptide, which mimics the action of the hormone at the bone and renal level, even if it does not affect intestinal absorption of calcium. The effects are therefore those of a paraneoplastic syndrome of various tumor origins with bone resorption and urinary retention of calcium. Bone metastases, prevalent in breast, lung, and myeloma tumors, can cause paracrine effects that stimulate the growth and function of osteoclasts, whose activity is responsible for bone resorption. Prostate tumors rarely produce hypercalcemia (3).

From the clinical point of view the signs are ambiguous and not specific. Pain is generally associated with bone metastases rather than hypercalcemia. Neurological and cardiac alterations, with shortening of the QT tract, are more straightforward (4). Non-ionized calcium is the parameter by which the extent of hypercalcemia is quantified (>1.29 mmol/L). If total calcium is measured, it should be corrected for hypoalbuminemia with the formula: total calcium in mg/dL + 0.8 (4 - albumin/dL). There is no precise correlation between laboratory data and symptoms of hypercalcemia (5). Values of parathormone peptide have an unclear meaning. Hypochloremia values support a diagnosis of humoral hypercalcemia. The values of parathormone are influenced by the calcium values and are not very useful (1).

a) Treatment

Hypercalcemia has a high mortality rate (50%) if not treated promptly. Therefore urgent intervention is required (table 1) (1). Hydration is the most important point because most patients with hypercalcemia are hypovolemic and oliguric. The restoration of adequate hydration and forced diuresis allows a quick and effective elimination of calcium. Diphosphonates reduce bone resorption, even if the effect is not immediate, requiring at least 2-4 days (2). Zoledronate can be infused more rapidly than pamidronate (15 minutes vs. 2 hours), but zoledronate is contraindicated in patients with renal impairment due to the risk of acute tubular necrosis. Pamidronate seems safer, although it may produce segmental nephrosclerotic toxicity (6).

Medication	Doses	Notes
Saline solution- plasmaexpanders	500-1000 ml	Rapid infusion Overload in cardiac patients
Furosemide	20-40 mg	After adequate hydration
Pamidronate	60-90 mg iv	Check renal function
Zoledronate	4 mg iv	Consider an alternative in patients with limited renal function
Calcitonin	4-8 IU / kg	Early tachyphylaxis
Corticosteroids Hydrocortisone	100 mg iv	Especially in patients with lymphoma, Check glucose levels
Denosumab		Approved for the prevention of bone metastases

Table 1. Treatment for hypercalcemia

Calcitonin administration reduces calcium values more rapidly than bisphosphonates (12-24 hours), but loses efficacy rapidly (7). Corticosteroids may reduce the release of cytokines and prostaglandins that activate osteoclasts, especially in humoral forms. They also inhibit calcitriol by macrophages (8). The activators of the nuclear factor κB (RANK), found on the surface of the osteoclast precursors and its ligands

(RANKL), produced by the lymphocytes and found on the surface of the osteoblasts, stimulate osteoclast differentiation able to begin the reabsorption (1). Parathormone and vitamin D stimulate the formation of osteoclasts by increasing the expression of RANKL on osteoblasts (9). Denosumab is a monoclonal antibody active on RANKL, and has potential indications in osteoporosis, the prevention of bone events, and hypercalcemia (10). Osminogenogenase, finally, a RANKL receptor and osteoclastic maturation inhibitor, corrects hypercalcemia in a faster way. (11).

Hyponatremia

Body fluids are divided into compartments that include the circulatory space, the interstitial space, and the intracellular space. Osmotic gradients move liquids to areas of greatest concentration. Sodium is the most important electrolyte for plasma osmolarity and indirectly represents how much water is present at the vascular level compared to the intracellular environment where most of the body water is located (12). Plasma sodium therefore corresponds to the distribution of water in the body compartments.

Hyponatremia translates how much excess water is present in relation to the amount of sodium, either by excess retention or by loss of sodium. The amount of body sodium (not the plasma sodium) determines the plasma volume. With a high amount of sodium, the volume is increased and the patient tends to accumulate fluids and getting edematous. On the contrary, plasma volume will be restricted and the patient will develop hypotension or in some cases hypertension. Low sodium plasma values may therefore be associated with hypervolemia, hypovolemia, or normovolemia, depending on the total sodium content (13). Hyponatremic euvolemic patients present a normal extracellular volume, that is a normal sodium body content, but a greater quantity of intravascular water. This picture is identified in cancer patients with the syndrome of inappropriate antidiuretic hormone secretion (ADH). ADH promotes renal reabsorption of water by binding to vasopressin 2 receptors, while the sensation of thirst is not sufficiently inhibited (14). The syndrome is especially observed in some lung tumors, pleura, thymus, and brain (15). In some cases, the cause is iatrogenic, for example from chemotherapeutics such as cisplatin, cyclophosphamide, ifosfamide, vinca alkaloids, and imatinib (16), although hyponatremia in these cases can be produced by other mechanisms of renal toxicity. Hyponatremia may be mild (131-135 mmol / L), moderate (126-130 mmol/L), or severe (<125 mmol/L). The influence

of hypoglycemia should be excluded. Sodium values can be corrected for hyperglycemia values with the formula: Plasma sodium in mmol/L + .016 (glucose in mg/dL - 100).

For a diagnosis of inappropriate secretion of ADH, adrenal insufficiency and hypothyroidism should be excluded. Actual osmolarity (urea/2.8 - measured osmolarity) must be less than 275 mOsm/kg of water and urinary osmolarity must be greater than 100 mOsm/kg (17). High values of urinary sodium (>40 mmol/L), hypouricemia (<4 mg/dL), and urea values of less than 10 mg/dL confirm the diagnosis (18).

- Treatment

The treatment of hyponatremia will depend on the cause and the plasma levels. In the case of very low concentrations (<125 mmol/L), there is a risk of cerebral edema and consequent neurological disorders. Probably because of the development of the symptomatology, the speed with which hyponatremia develops is much more important. Severe chronic hyponatremia is tolerated better than with less altered values but with an acute development of hyponatremia (15). The treatment involves the administration of hypertonic solutions in the most serious cases or saline solutions. The correction should take place gradually to avoid the pontine myelinated lesions described as a consequence of narrowing of the brainstem cells (19). The paucisymptomatic forms are treated with water restriction. Demeclocycline, a tetracycline capable of inducing renal insipid diabetes, can reverse the syndrome (20). Vaptans bind vasopressin V2 receptors at the renal level, inhibiting their action. Oral tolvaptan (15 mg/day) allows the correction of hyponatremia by promoting an increase in water diuresis (21).

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CHAPTER TWENTY-SIX

END OF LIFE CARE

The aim of modern palliative care is to control suffering regardless of the stage of cancer disease, while ensuring and maintaining comfort and dignity even during the last days or hours of life. As with any aspect of palliative care, dying care requires a diagnostic and prognostic evaluation, and symptomatic treatment. Cancer death is generally not sudden or catastrophic and a diagnosis of a process initiated is not always easy. An debilitated patient, no longer able to swallow effectively and with an altered level of consciousness, generally offers a fairly simple picture of a process of death that will end in a few hours or a few days. Some very simple factors have been taken into account that allow one to predict death within one week. These include the reduction of blood pressure and the increase in heart rate, indices of vegetative dysautonomia and the expression of inflammatory collapse, a very low Karnofsky value, high intensity of anorexia and dyspnoea (1). These signs should lead to the starting of a more specific communication on the course of events with family members. This approach will re-modulate the level of expectation in relation to reality (see chapter 3). The diagnosis of the final phase is very important for the involvement of the family members in the consequent decisions and to prevent requests or expectations that are irreconcilable with reality. Sometimes some ambiguous attitudes feed the uncertainties, facilitating unconsciously hostile attitudes from family members who have notreconciled themselves to the inevitable events that are about to approach. Therefore, routine investigations or treatments should be suspended and the indication not to resuscitate should be discussed and documented.

However, in a non-specialist environment, this phase is not always identified until the last 24 hours, and treatments are often used only to postpone the final event, compromising the quality of the last days with futile and disproportionate treatments up to the end of an admission to intensive care. On some occasions, not so rarely (25%), patients already followed by a home palliative care team can be admitted to hospital in the last days of life. In particular, younger patients with head-neck tumors,

with a history of alcoholism, those followed for a short time at home, or those who did not have a wife as a caregiver, had a higher risk of being transported to hospital, where they died in about 10 days. The most frequent cause of hospitalization was the presence of dyspnea (2).

Most common symptoms in imminent death

The most common symptoms that occur in the terminal phase include agitation, often with over-expression of pain and suffering, dyspnea, and abundant pharyngeal laryngeal secretions. Anorexia and fatigue, generally widely present, are not perceived as stressful symptoms at this stage. Dysphagia, constipation, urinary retention, hemorrhage, and convulsions, although more rarely, can appear in the terminal phase and lead to important care problems in the last hours of life.

In patients followed at home, in the last two hours of life the most frequent clinical events were death rattle, dyspnea, and agitation (3). While most patients, about 2/3, gradually doze off showing no particular signs of physical distress, as a consequence of the worsening of metabolic and neurological conditions, many others exhibit a very dramatic and demanding transition phase which requires specialist intervention. The perception of pain can change in the last days, due to the appearance of delirium, which amplifies all the stimuli, not only the painful ones. The neuroexcitatory effects of opioids, such as myoclonus, hyperalgesia, and hallucinations, are very common in the dying patient. Factors predisposing to the development of neurotoxicity are represented by high doses of opioids, with substantial dose increases in the last days, oliguria, dehydration, advanced age, and the use of other centrally acting drugs. Disperceptions and cognitive alterations are very typical both for well-known causes (see chapter 21b), but also for an inflammatory explosion that inexorably dominates the last days of life. Added to this, there is the anguish of the perception of imminent death and a subsequent psychological distress.

Delirium is a multifactorial syndrome characterized by alterations of consciousness and attention with a fluctuating pattern. In the terminal phase it appears in most patients, even if it manifests itself clinically in a completely individual manner (4), depending on the prevalence of hypoactive, hyperactive, or mixed forms.

The hypoactive forms accompany a relatively serene end of life and require fewer interventions than the hyperactive forms, which are much more stressful. Delirium is inevitably associated with the loss of control, autonomy, and inevitably individual dignity. An appropriate and timely

treatment is mandatory for such forms. While in some cases a treatable cause is recognized, and delirium is reversible or in any case can be limited, in the terminal phase, the appearance or aggravation of delirium requires a different approach from that described in the dedicated chapter (chapter 21b). Generally these patients are already receiving a symptomatic treatment to mitigate the symptoms, or on the contrary delirium can arise late, exclusively in the final phase. Neurotoxicity, infections, dehydration, hypoxia, metabolic alterations or other brain injuries, and amplified sensations in the presence of cognitive impairment (for example bladder distension) find a favorable tissue in the enormous inflammatory state that initiates the process of death. Dyspnea shows similarities to pain: it is an individual subjective sensation determined by physical and psychological components. In most cases this experience is already present in the final phase and treated with causal and symptomatic drugs. Therapeutic control may be lost in the last few days or the causes of the symptom may be aggravated by the aforementioned reasons, above all due to the patient's serious psychological state.

Palliative sedation

The process of death can take on dramatic contours, beyond the predictable family distress due to the loss of their loved one. In about half of patients the process of death is accompanied by the appearance of intractable symptoms in the last days of life that negate good care. In the absence of effective causative or symptomatic means, it is often necessary to weaken the level of consciousness to avoid the intense suffering associated with these symptoms. The use of sedation is quite variable in literature, also depending on the different care settings. At home, for example, timing cannot always be completely efficient, depending on the appearance of symptoms. Precisely for this reason, greater capacity will be needed to prevent events. In a more intensive care setting, the frequency is higher (50%), both for the selection of hospitalized patients and for the possibilities of prompt intervention (5).

End-of-life sedation refers to the use of sedative drugs to control intractable symptoms in the last days of life in the dying patient (4, 6, 7). The term "controlled sedation" for intractable symptoms in the dying patient more accurately expresses the mode, purpose, needs, and context. In particular, it includes the various levels of sedation (mild, deep, intermittent, or continuous, how it is monitored, and administration by expert personnel) (5). The term sedation is implicit and is defined as the administration of drugs used to decrease the level of consciousness as

needed in different or sequential modes and contexts (controlled). Intractable symptoms refer to a clinical condition that does not respond to a standard treatment for the control of symptoms that are causing great distress to patients and for which sedation is the last available resource. Finally, "dying patient" is used to identify the prognostic context [5].

The most frequent symptoms that require sedation are delirium and dyspnea (5-7), often accompanied by a strong component of psychological and existential distress. Other symptoms such as pain or nausea, reported in pioneer studies, are in fact rarely called into question. Very often the painful manifestations are consistent with a previous lack of control, generally due to a very late admission to palliative care services, or more often they represent a generalized sensorial hyper-expression, typical of a state of delirium.

Starting palliative sedation is a very delicate decision for the obvious ethical implications. Only a continuous symptom assessment will make it possible to make a decision. The presence of psychological-existential distress for example is at the periphery and should be used as an indication only in exceptional circumstances, once all possible weapons are exhausted. This is one of the few cases in which the sedation request comes from the patient (8). Thus, sedation may be transitory and partial initially in an attempt to interrupt the vicious distress-request circuit. This also applies to bridging conditions where death does not appear imminent despite the presence of intractable symptoms. A reassessment of the case after removing the significantly anxious state allows the right decision to mature.

In most cases the level of suffering is such that the patient in these phases is hardly competent and there is often an urgency in the treatment of symptoms, for example in patients with progressive dyspnea, massive bleeding, agitation, and delirium. Therefore, the presence and the role of the family are fundamental. In the best situations, the family members have been informed in advance of the dying process and of the possible need to control the situation in the last hours of life, if necessary, to ensure a transition without apparent suffering. For this reason, attempts to communicate the process of death and assent with family members must be anticipated in relation to the clinical course and the predictors examined.

In some cases there is not the same level of maturation of facts and reality among the family members. Team members should explain the need to change strategy according to the patient's interest. An interview with all the relatives present is sometimes necessary to smooth out any problems and clarify uncertainties. The request for informal written

consent is unpleasant and demanding because it has the meaning of an assumption of responsibility. The explanation that it is a medical act contemplated and due in that case is more than enough to regularize the emotions and make the decision more acceptable, however shared in the interest of the patient. Often the sedation request comes directly from the family members and rarely from the patients, who in most cases are not able to provide consent in these phases.

Unfortunately, there is some confusion in the adoption of terminology concerning end-of-life issues. This often leads to numerous errors, particularly in public opinion, the media, and in different cultural contexts. In some cases, doubts may arise in clinical practice that make final decisions particularly dubious and ambiguous. It has been observed, for example, that many doctors recognize the intention to shorten life intentionally, particularly with the use of certain categories of drugs in which the side effect is used to induce sedation. The use of opioids with the sole purpose of inducing sedation, for example, is out of place, as they cause deep sedation together with considerable respiratory depression. However, the combined use of opioids with sedative drugs such as midazolam, with the aim of maintaining analgesia or reducing the sensation of respiratory distress in the final phase, recognizes a correct therapeutic attitude. The differences between palliative sedation and other end of life issues, which may be confounded or in some cases may overlap the borders of such an approach in the suffering patients in the last days of life, also from a legal and ethical point of view, are listed in table 1.

	Murder	Suicide	Assisted suicide	Euthanasia	Palliative sedation
Aim	death	death	death	death	symptom relief
Consensus	no	yes	yes	yes	yes-delegate
Timing	any	any	any	any	end of life
Administration	murderer	patient	physician	physician	palliative care team
Planning	planned	planned	planned	planned	when necessary
Decision	murderer	patient	patient	patient	team-family-patient
Drugs–dosing	lethal	lethal	lethal	lethal	tailored

Table 1. Differences between palliative sedation and other modalities of determining death

It is evident how different are the aims and the modalities to give drugs with a palliative purpose. Some elements, shown in table 2, must be taken into consideration in the dying patients with intractable symptoms that are candidates for sedation.

- Timeliness - Setting - Experience - Culture - Environment - Communication

Table 2. Elements to be taken into consideration in the dying sick with intractable symptoms and sedation candidates

Before starting sedation it is essential to provide an environmental remediation that involves the use of soft lights, avoiding annoying noises and beeping, and includes the presence of a family member nearby, with the aim of maintaining a serene and peaceful atmosphere to promote sedation and avoid sensory stimuli able to aggravate the symptoms, considering the particular vulnerability of the patient (table 3).

-Room with one bed -Avoid skin, sound, and visual stimuli -Caress without causing annoyance -Humidify the lips -Preventive urinary catheterization -Do not force evacuation -Suspend painful dressings -Suspend drugs that are not useful -Small number of relatives in the room

Table 3. Basic measures to promote sedation

The care setting should be taken into consideration. While in the hospice environment a dedicated room is available that lends itself exactly, at home, overcrowding should be avoided in often very small rooms. In the case of a hospital, one should organize a similar controlled context, providing a single room.

Sedation is divided into several levels, which should be proportional to clinical needs. Intermediate or intermittent sedation is often used in

emergency conditions, when the time for a shared discussion with family members has not yet matured. Transient sedation, used for painful procedures, has nothing to do with end-of-life circumstances. Complete abolition of consciousness is not always necessary to control symptoms. In some cases, in fact, a mild sedation can still allow contact with adequate symptom control. In other cases, the level of sedation is managed to particular cases such as the temporary resolution of symptoms waiting for an unlikely recovery, or the arrival of distant family members. These circumstances corroborate the concept of "controlled" sedation in which the level of lowering the state of consciousness depends on a dose of drugs individually tailored to the circumstance. This requires a great confidence in the use of drugs and the assessment of the level of consciousness, in relation to the desired level of control of the symptoms that requir sedation. In some cases the fatal event (massive bleeding or thromboembolism) appears so quickly that it nullifies a timely sedative intervention.

Pharmacological treatment

Midazolam, a short half-life benzodiazepine, is the most flexible hypnotic drug and therefore more suitable for reducing or eliminating the state of consciousness. The manageability in the administration of dosages, as well as the possibility of using it also subcutaneously, make it the drug of first choice. After the administration of a bolus-priming of 2-3 mg to obtain a rapid sedation level, a continuous infusion can be started at a rate proportional to the effect obtained with the bolus and then re-evaluated after a few hours of infusion according to the set objective, the monitoring of the level of consciousness, and refractory symptoms that indicated the need for sedation. Despite a careful titration of the dosage there is often an inevitable loss of communication with the patient (5). The doses are variable (20-70 mg/day on average), with even higher dosages especially in young people, particularly in patients already receiving sedative or antipsychotic drugs unsuccessfully, or in the case of prolonged sedations (5, 6, 8). It is also possible to practice sedation at home, even if all the necessary measures are not always possible and the level of monitoring is inevitably lower (7, 9). The use of sedation is variable, generally less at home, where even the timing is more difficult, compared to settings with beds, where possibly there are hospitalized patients in worse conditions that require medicalization in the last days of life (5).

In these phases, hydration, which should always be attentive to a good control of the symptoms, loses its function and the lack of liquid intake does not lead to the appearance of symptoms such as thirst. Therefore,

with the onset of sedation, forced hydration should be suspended or minimized for the delivery of the necessary drugs (5). In about half of patients, death rattle will appear, a consequence of the inability to swallow and cough pharyngeal and tracheal secretions (10). This noise has a major impact more on family members than on the patient, who is probably unable to feel this sensation. The treatment of death rattle is based on the use of anticholinergic drugs. However, it is evident that the presence of already formed secretions is difficult to reverse. This explains how in the literature the effectiveness of anticholinergics is quite variable. Indeed, in all patients with spontaneous or sedation-induced loss of consciousness, hyoscine butylbromide should be administered as a pre-emptive measure to prevent secretions from forming every time a low level of consciousness develops, either spontaneously or with palliative sedation. An early administration of hyoscine butylbromide provided an effective method to prevent death rattle in most patients in comparison with the use of the same drug once death rattle had been developed (11). In these cases, in selected environments the secretions can be gently aspirated with a precise sedation and then a treatment with anticholinergics could be started (12).

Opioid administration should be continued by modifying the route of administration, with preference for the parenteral route or the transdermal route. If the leading symptom requiring palliative sedation is dyspnea, the doses should be increased compared to those previously needed for pain control. Table 4 shows the methods for optimal sedation. On the contrary, the use of opioids to induce sedation should be avoided, because the inevitable side effect could only be the hastening of death, an effect unfortunately deliberately sought in some cases (13). Indeed, in some cases the state of agitation could further worsen. Therefore one should use the drugs according to the main indications: benzodiazepines for sedation, analgesics for pain or dyspnea, and so on.

- Midazolam 15-30-45 mg/day
- Convert opioids to the parenteral route
- Scopolamine butylbromide 60 mg/day
- In the presence of death rattle, if possible, gentle suction of secretions, before starting anticholinergics.
- Maintain the use of diuretics
- Reduce fluids (<250 ml/day)
- In the presence of dyspnea, increase the dose of opioids

Table 4. General treatments concomitant with sedation

The obvious consequence of sedation is the loss of communication with the dying person. Adequate and repeated monitoring makes it possible to adjust the dose of sedatives to the circumstances and to the desired level of sedation to avoid hyper-sedation or reverse sub-sedation conditions (14). An underestimation of these aspects mortifies medical practice, often trespassing into euthanasia, as often happens in some countries where doctors expect a shortening of life with the administration of drugs. The double effect doctrine, often cited to justify sedation, risks fueling doubts about sedation (see chapter 2). It is instead widely documented that sedation does not cause death if carried out with care, and above all does not accelerate the process of dying (15).

The Glasgow Coma Score, inherited from use in intensive care, has the disadvantage of determining potentially painful stimuli to solicit patient answers (13), risking a compromising of attempts to becalm the patient. There are other tools that are much more appropriate and reliable, such as the Richmond Agitation Sedation Scale, the Ramsay sedation scale, and the community capacity scale. The monitoring intervals are variable according to the circumstances and the environment in which it is practiced. The Richmond Agitation Sedation scale, the most used and reliable, is shown in table 5 (15).

+4	Agitated, violent, dangerous
+3	Very agitated, you remove pipes and catheters, aggressive
+2	Agitated, non-finalistic movements
+1	Anxiety and uncoordinated movements, but not aggressive
0	Calm and awake
-1	Sleepy but awakening to contact or verbal call
-2	Slight sedation with brief awakenings to verbal call
-3	Moderate sedation, movements or eyes open to verbal recall
-4	Deep sedation. No response to the voice, but movements or eye openings to the physical stimulus
-5	Not arousable to stimuli

Table 5. Richmond Agitation Sedation Scale.

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