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KEY POINTS FOR THE APPROPRIATE USE OF OPIOIDS IN CHRONIC NON-CANCER PAIN

The treatment of chronic non-cancer pain (CNCP) with opioids has increased progressively over the years, with treatment regimens based on very limited evidence. With the arrival of transmucosal fentanyl preparations on the market, the situation has deteriorated, mainly due to the inappropriate use of these drugs. Despite the lack of evidence supporting use of opioid therapies for CNCP for a duration longer than 6 months, there are a growing number of patients who receive treatment at high doses for more than two years and in combination with other medications that cause confirmed safety problems. This situation has resulted in a major challenge for healthcare services in the form of treatments with a non-specified duration, lack of capacity to assess outcomes, and associated adverse effects such as hyperalgesia, physical dependence, or addiction. OBJECTIVE The objectives of this report are: (1) to formulate recommendations and protocols that guarantee the appropriate duration and use of opioid therapies to prevent their serious side effects; (2) to determine the information required before an opioid is prescribed in relation both, to the patient and the medication selected; (3) to propose tools for the adequate follow-up of patients.
KEYWORDS Opioids, chronic pain, pain management.

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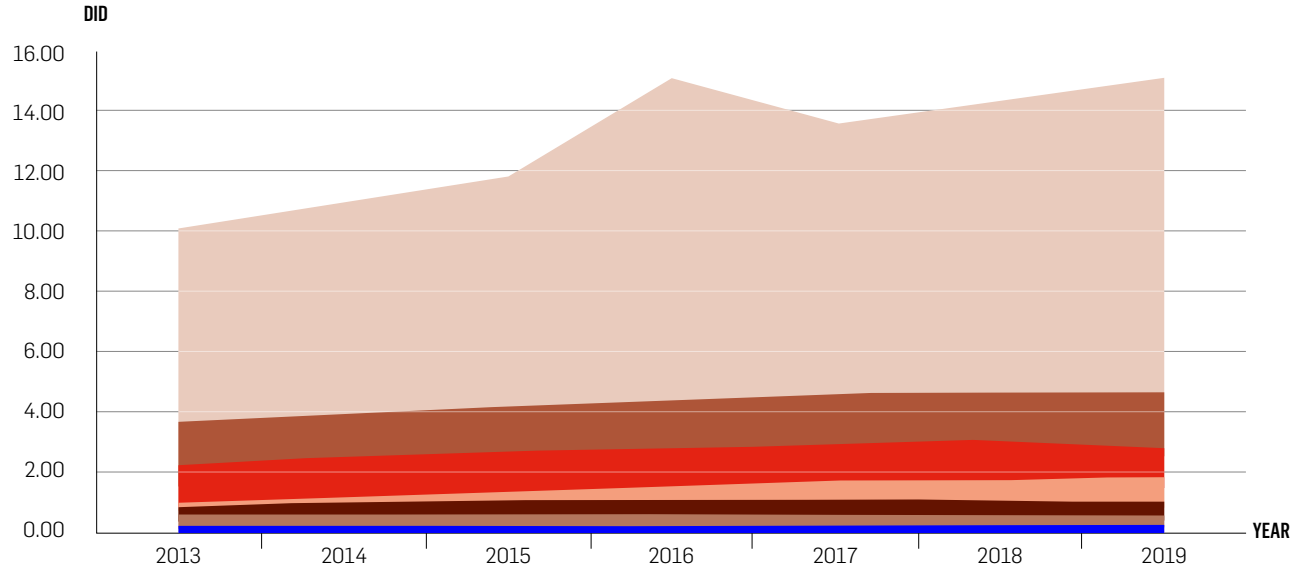
The problem

In the last few years, we have witnessed a national and international increase in the supply of and demand for opioids. The prescription of "weak" opioids, which contain tramadol, is nearing that of non-steroidal anti-inflammatory drugs (NSAIDs), whereas the use of strong opioids has seen a substantial increase[1,2]. Fentanyl is one of the opioids which use has increased most dramatically in the world.

Opioids are most often prescribed for the management of chronic non-cancer pain (CNCP), which includes a variety of syndromes and disorders for which the effectiveness of these drugs has not been validated and is controversial in many cases. Opioid analgesics are not the first-line treatment for either nociceptive or neuropathic pain management[3] (algorithms 1 and 2). In fact, there is evidence that in some cases they may be contraindicated[4].

In the management of cancer patients, in whom the effectiveness of opioid analgesics is well documented, the average daily dose to reach therapeutic effects does not exceed 60 mg of morphine equivalent dose (MED). Nevertheless, in CNCP, average doses are higher, with a mean of up to 92 mg MED in controlled clinical trials[5], which poses some risks to the patient and requires close monitoring.

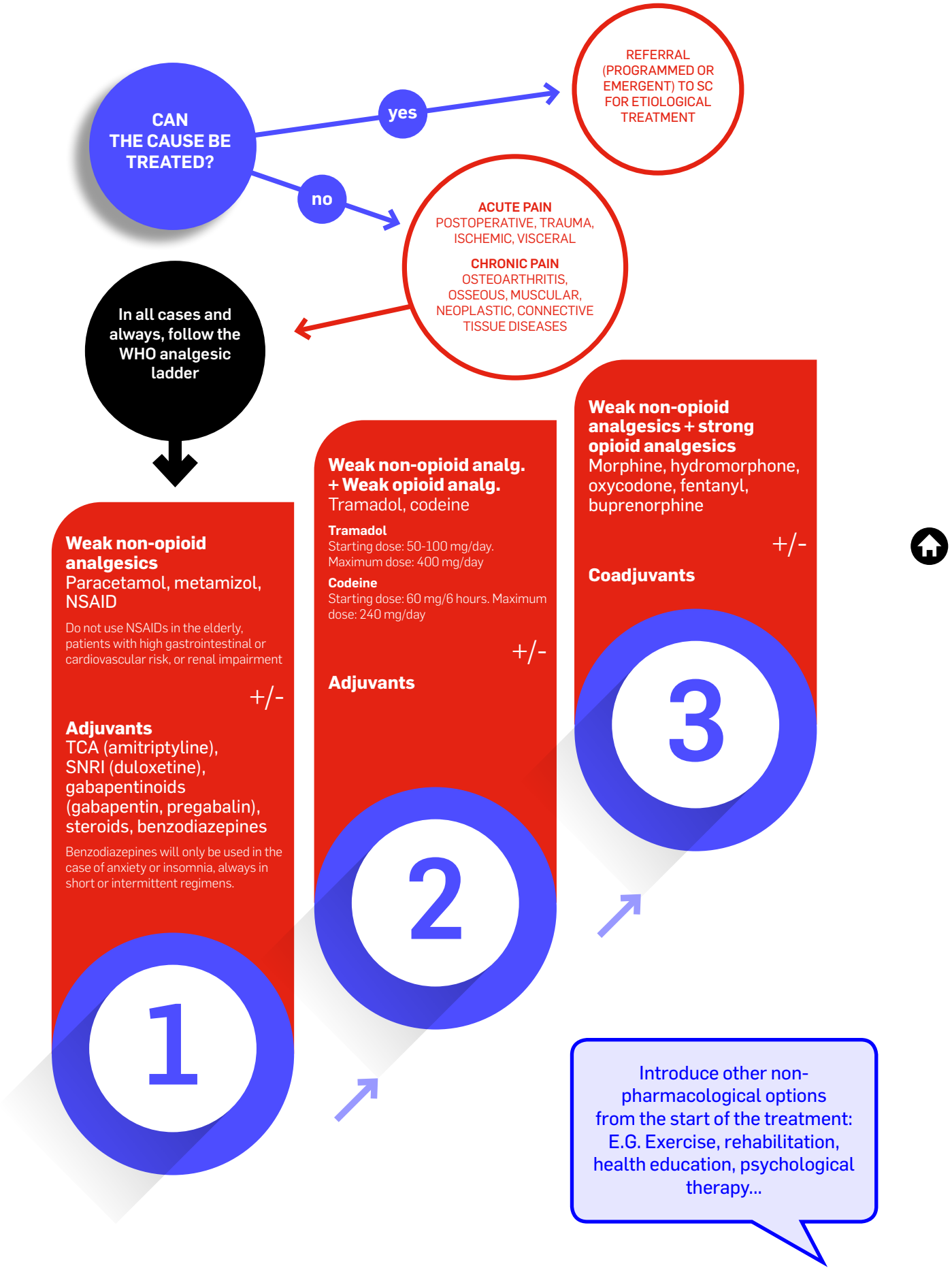
Figure 1. Opioid use per prescription in Navarra.



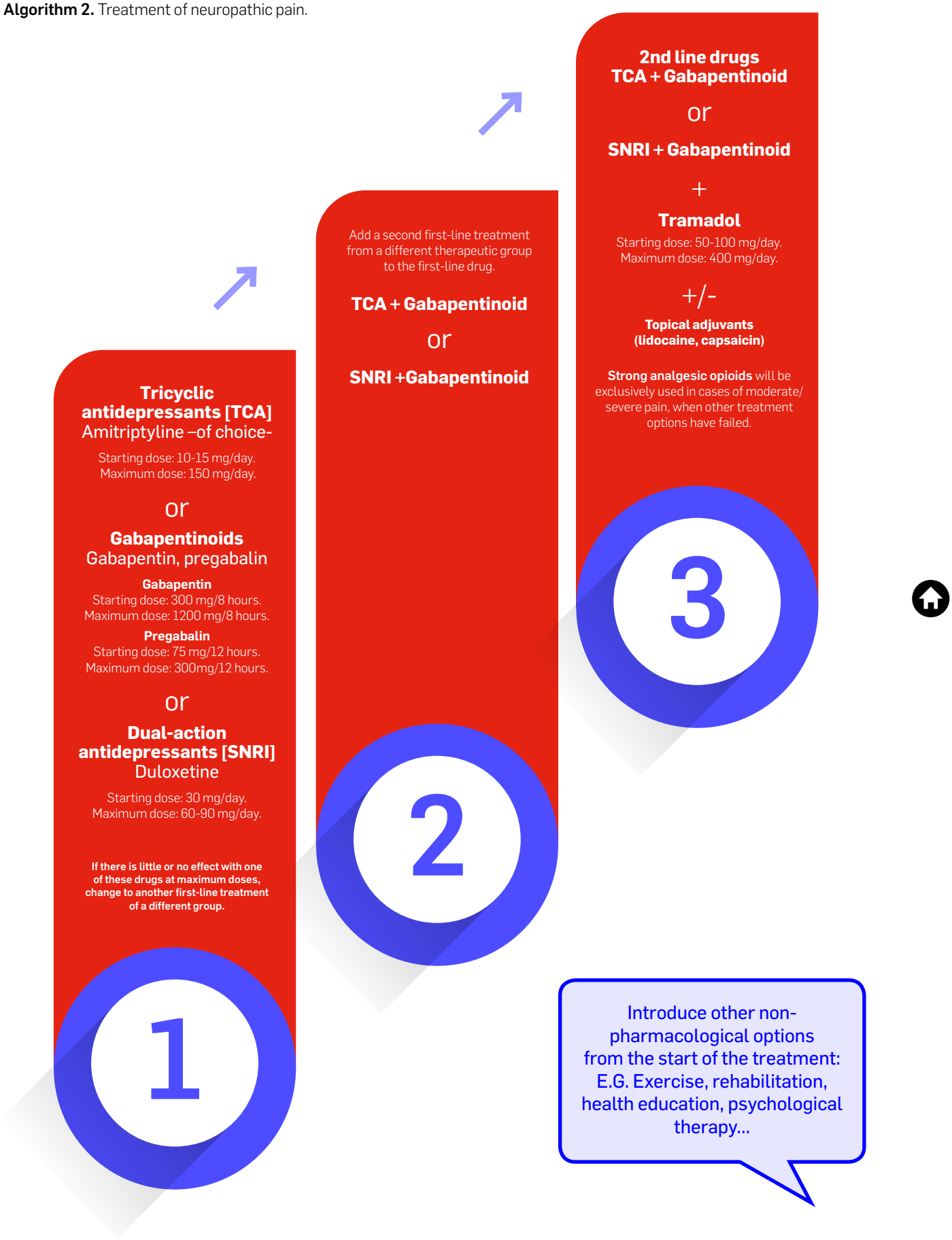
	2013	2014	2015	2016	2017	2018	2019
Tramadol	6.40	7.07	7.63	10.70	9.07	9.70	10.41
Fentanyl	1.42	1.54	1.60	1.60	1.66	1.75	1.82
Codeine	1.35	1.31	1.35	1.32	1.20	1.24	1.09
Tapentadol	0.08	0.16	0.28	0.43	0.61	0.74	0.78
Oxycodone	0.24	0.33	0.41	0.49	0.52	0.51	0.50
Buprenorphine	0.46	0.48	0.46	0.43	0.38	0.32	0.32
Morphine	0.16	0.16	0.16	0.17	0.20	0.20	0.21
Hydromorphone	0.03	0.02	0.02	0.02	0.02	0.02	0.02
Pethidine	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Source: Database of prescription billing. SNS-O

Algorithm 1. Treatment of nociceptive pain.



Algorithm 2. Treatment of neuropathic pain.



As a result of the rise in the use of opioids, the incidence of side effects has increased. Apart from the already known problems (e.g. gastrointestinal, cardiovascular, cognitive), other side effects are becoming more frequent (opioid-induced hyperalgesia[6], serotoninergic syndrome[7,8], abuse and addiction[9]), which are more marked in non-cancer patients with prolonged treatments. Altogether, these problems represent a public health concern that can be aggravated by concomitant medications such as depressants of the central nervous system (e.g. benzodiazepines)[10,11], or alcohol[12].

Historically, there has been a sort of "opiophobia" worldwide, and the use of opioids has been systematically linked to the negative perspective of cancer. The turning point of this view occurred in the 90s, when the American Pain Society started to consider pain as the fifth vital sign and recognized that the pain control strategies used until then were not optimal. Moreover, in 1995, Oxycontin® was released to the market with the indication for CNCP treatment and was supported by a strong marketing campaign that highlighted its safety and minimized its addictive potential. In this way, opioid analgesics became the cornerstone of the treatment of severe pain, and the WHO started to consider the rate of opioid prescriptions in a country as a relevant indicator of the quality of care in relation to pain. Specific units for the treatment of pain were created (Palliative Care Units and Pain Units) and numerous administrative barriers regarding the prescription of these drugs were eliminated. As a result, physicians are less reluctant and feel free to prescribe opioid analgesics.

To this we must add the dramatic increase in the production of opioids. Novel and increasingly powerful drugs, as well as new routes of administration have been developed, with high prices.

In view of the foregoing and considering the loose criteria currently used by healthcare services for the administration of opioids (i.e. to palliate pain and suffering), the use of opioids is placing patients at risk, unless appropriate use by all the parties involved is ensured.

This report has three main objectives:

- To provide appropriate tools for selecting candidates for first opioid prescription.
- To provide tools for adequate follow-up of patients using opioids for periods longer than three months to determine whether the treatment is effective or not.
- To review regimens for a progressive reduction of the dose of opioids to ensure an appropriate rotation of these drugs.

Types of opioids, dosage, routes, titration, and morphine equivalence

We often use the terms "opiates" or "opioid" interchangeably; however, there are differences between the two terms. The term "opiate" refers to alkaloids present in opium, which is extracted from poppy (Papaver somniferum) capsules and, by extension, to chemicals derived from morphine. On the other hand, the term "opioid" refers to endogenous or exogenous substances with analogous effects to those of morphine and with intrinsic activity on opioid receptors present in the central nervous system and gastrointestinal tract. Hence, all opiates are opioids but not all opioids are opiates. Thus the term "opioid analgesics" is more appropriate, at it includes all concepts.

Opioid analgesics are drugs that predominantly act on the opioid receptors of the nervous system, mimicking the analgesic action of endorphins. The first opioid analgesic was morphine, which can be naturally obtained from poppy capsules, and is still the opioid of reference. Subsequently, other natural, semisynthetic and synthetic opioids have been obtained.

Table 1 shows the main opioid analgesics available in Spain, with dosage as indicated on the data sheet[13] and recommendations for starting dose adjustment (titration)[14,15]. Due to the special properties of transmucosal fentanyl, this formulation is not included in the table and will be discussed below.

Table 1. Analgesic opioids marketed in Spain.

	Route	Dosage	Maximum dose	Titration		
				Starting dose	Min. interval to increase the dose	Dose increments
Morphine	SC or IM	Ad: 5-20 mg/4 h Children: 0.1-0.2 mg/Kg/4h (max. 15 mg/24 h)	Not available	2.5-5 mg/4 h, if required (max. 20 mg/d)	Oral/SC ratio = 2:1	
	Oral IR	> 13 a: 10-20 mg/4-6 h 5-12 a: max. 5-10 mg/4 h 1-5 a: max. 2.5-5 mg/4 h	Not available	5-10 mg/4 h, if required (max. 40 mg/d)	7 d	5-10 mg/d
	Oral ER	Ad: 30 mg/12 h Children: 0,2-0,8 mg/kg/12 h	Not available	10 mg/12 h	Min. 2 d (14 d recommended)	5-10 mg/d
Hydromorphone	Oral ER	Ad (> 18 a): 4-8 mg/24 h	8 mg/24 h	4 mg/24 h	Min. 4 d (14 d recommended)	4 mg/d
Oxycodone	Oral IR	Ad (> 20 a): 5 mg/4-6 h	Not available	5-10 mg/6 h	7 d	5 mg/d
	Oral ER	Ad (> 20 a): 5-10 mg/12 h	Not available	10 mg/12 h	Min. 2 d (14 d recommended)	5 mg/d
Codeine	Oral IR	28 mg (1 comp)/6 h 15-20 mg (15 ml) /6 h	240 mg/d (max 3 d)	15-30 mg/4 h	7 d	15-30 mg/d
Pethidine	IM or SC	25-100 mg/4h	400 mg/24 h	Initial dose adjustment (titration) is not recommended with this opioid		
Fentanyl	Transdermal (patches)	> 16 y tolerant to opioids: 12-25 µg/h every 72 h	300 µg/h every 72 h	Initial dose adjustment (titration) is not recommended with this opioid. Patches cannot be cut.		
Buprenorphine	SL	0.2 mg/8 h	0.2-0.4 mg/6-8 h	Not available		
	Transdermal (patches)	Ad: TPW/O: 35 µg/h every 72-96 h TPCO: individual adjustment	70 µg/h every 72 h (if additional analgesia required: 0.2-0.4 mg SL / 24 h)	5 µg/h every 7 d (patches can be cut)	7 d	5 µg/h every 7 d
Tramadol	Oral IR	Ad and children > 12 y: 50-100 mg every 6-8 h	400 mg/d	25 mg once a day (slotting the tablet)	4 d	25 mg/d
	Oral ER	Retard formulations every 12 h: 50-200 mg/12 h Retard formulations every 24 h: 100-300 mg/24 h Retard BID formulations: 75 mg/12 h	400 mg/d	100-150 mg/24 h	5-7 d	75-100 mg/24 h
Tapentadol	Oral IR	Ad: 50 mg/4-6 h	700 mg first day and 600 mg/d for maintenance	50 mg/4-6 h		50 mg/4-6 h
	Oral ER	50 mg/12 h	Not recommended > 500 mg/d	50 mg/12 h	3 d	50 mg/12 h

IM Intramuscular
IR Immediate-release
ER Extended-release
SC Subcutaneous
SL Sublingual
y Years
Ad Adults
TPW/O Treatment of patients without background opioid regimen
TPWO Treatment of patients with background opioid regimen

There is wide variability between subjects in the doses of opioid analgesics required to treat pain appropriately. For this reason, numerous systems and reference tables have been proposed to calculate equianalgesic doses between different opioids. In general, these tables are based on conversion factors established in relation to morphine, and propose calculations based on total daily doses (MED = morphine equivalent dose per day). Thus, it is always necessary to perform calculations based on the dose that a patient receives in 24 hours, and then distribute the equivalent dose of the new opioid throughout the day, with a dosage adjusted in accordance with its pharmacokinetics[16].

The calculations obtained from these tables do not replace clinical judgment and experience, and the clinical condition of the patient must be considered in all cases, as well as renal and liver function, the intensity and nature of pain, and potential drug interactions.

Tables 2 to 4 include some guidelines for the selection of the most appropriate starting dose, and for titration from that dose until the desired effects are obtained, thereby minimizing their adverse effects. These tables can also be useful to make us aware of the total daily dose of opioids being prescribed. In the treatment of CNCP, doses < 40 mg MED are considered low; doses between 41 and 90 mg MED are moderate; and doses ≥91 mg MED are high[17].

Table 2. Approximate equivalent doses of the most commonly used opioid analgesics[18].

From	Opioid A	to	Opioid B	C.F.	Example
	Morphine OR		Morphine SC	+ 2	30 mg morphine OR = 15 mg morphine SC
	Morphine OR		Oxycodone OR	+ 2	30 mg morphine OR = 15 mg oxycodone OR
	Morphine OR		Hydromorphone OR	+ 7.5	30 mg morphine OR = 4 mg hydromorphone OR
	Tramadol* OR		Morphine OR	+ 10	100 mg tramadol OR = 10 mg morphine OR
	Tapentadol* OR		Morphine OR	+ 2.5	50 mg tapentadol OR = 20 mg morphine OR
	Codeine OR		Morphine OR	+ 10	240 mg codeine OR = 24 mg morphine OR
	Tramadol* OR		Tapentadol* OR	+ 4	200 mg tramadol OR = 50 mg tapentadol OR
	Tapentadol* OR		Oxycodone OR	+ 5	50 mg tapentadol OR = 10 mg oxycodone OR

(*) Analgesia partially mediated by opioids. Increased risk of potential opioid-related side effects when changing to other opioids.

C.F. Conversion factor

Table 3. Conversion of the most commonly used opioid analgesics to oral morphine equivalents[19].

	Route	C.F.	50 MED	90 MED
Morphine[13]	SC or IM	2	25 mg/d	45 mg/d
	Oral	1	50 mg/d	90 mg/d
Hidromorphone[19,111]	Oral	5	10 mg/d	18 mg/d
Oxycodone[19,111]	Oral	1.5	33 mg/d	60 mg/d
Codeine[19,111]	Oral	0.15	334 mg/d	600 mg/d
Pethidine[13]	IM or SC	0.3	167 mg/d	300 mg/d *
Fentanyl (µg)[112]	Lozenge, sublingual, or oral	0.13	385 µg/d	692 µg/d
	Oral film	0.18	278 µg/d	500 µg/d
	Nasal spray solution	0.16	312 µg/d	562 µg/d
Tramadol[19,111]	Oral	0.2	250 mg/d	450 mg/d *
Tapentadol[19,111]	Oral	0.4	125 mg/d	225 mg/d

(*) Over the maximum dose.

C.F. Conversion factor
50 MED Equivalent dose to 50 mg/d oral morphine
90 MED Equivalent dose to 90 mg/d oral morphine

Table 4. Approximate equivalent doses of transdermal opioids to oral morphine[18].

Opioid	Dose (µg/h)	MED
Buprenorfina	35 µg/h every 3-4 d	63-97 mg/d
	52,5 µg/h every 3-4 d	95-145 mg/d
	70 µg/h every 3-4 d	126-193 mg/d
	140 µg/h every 3-4 d	252-386 mg/d
Fentanilo	12 µg/h every 3 d	30-59 mg/d
	25 µg/h every 3 d	60-89 mg/d
	37 µg/h every 3 d	90-119 mg/d
	50 µg/h every 3 d	120-149 mg/d
	62 µg/h every 3 d	150-179 mg/d
	75 µg/h every 3 d	180-239 mg/d
	100 µg/h every 3 d	240-299 mg/d
	125 µg/h every 3 d	300-359 mg/d
	150 µg/h every 3 d	360-419 mg/d
	175 µg/h every 3 d	420-479 mg/d
	200 µg/h every 3 d	480-539 mg/d
	225 µg/h every 3 d	540-599 mg/d
	250 µg/h every 3 d	600-659 mg/d
	275 µg/h every 3 d	600-719 mg/d
	300 µg/h every 3 d	720-779 mg/d

Doses in white cells are not recommended in CNCP.

Indications, non-indications, contraindications

There is clear evidence supporting the effectiveness of opioids in the management of acute severe pain, post-surgical pain, and cancer pain. In comparison with placebo, opioid treatment is associated with short-term pain mitigation, although the follow-up period did not exceed six weeks in the majority of controlled randomized trials. No studies assessing the effects of opioids on pain, functionality or quality of life when used over a period of one year have been found[20]. Also, there is increasing evidence that opioids have limited effectiveness in the treatment of CNCP[9].

Therefore, opioid analgesics are not first-line drugs for the treatment of CNCP and should only be used in patients with moderate/severe pain who are unresponsive to other drugs or strategies (including minimally invasive techniques), and when a short-term reduction of the main cause of pain is expected. In this setting, an individual risk-benefit assessment is required.

Long-term treatment (≥ 6 months) with opioids should only be maintained in patients who have satisfactorily responded after a trial period and who have shown mild, temporary or no adverse effects, and always with adequate follow-up and regular visits.

It should be taken into account that the appropriate management of this type of pain implies an integrated and multidisciplinary approach adopted since the start of the treatment.

Regarding the type of pain, although there are no absolute contraindications for the use of opioids, there is evidence supporting the recommendation to avoid their use in some cases 4 (Table 5).

Long-term opioid treatment can be an option for patients with chronic back pain, chronic osteoarthritis, and chronic neuropathic pain, as long as they have experienced a clinically significant reduction in pain or in physical deterioration after a trial period. For the remaining types of CNCP, the therapeutic approach must be individualized due to the lack of scientific evidence.

Table 5. Possible indications and non-indications in the opioid analgesic treatment of CNCP.[4]

INDICATED*	
With scientific evidence (treatment duration: 4-12 weeks)	**Without scientific evidence (insufficient data)**
Diabetic polyneuropathy.■ Postherpetic neuralgia.■ Other syndromes of neuropathic pain (phantom limb, spinal cord injury, radiculopathy, HIV-induced polyneuropathy.■ Osteoarthritis.■ Chronic back pain.■ Rheumatoid arthritis (time limited to 6 weeks).	Secondary headache (vascular disease, intracranial disorders). Significant osteoporosis (vertebral fractures). Rheumatic diseases (lupus, spondyloarthritis). Chronic postoperative pain (after thoracotomy, sternotomy, mastectomy, abdominal surgery, facial surgery). Pain in the limbs due to ischemic arteriopathy or veno-occlusive disease. Chronic pain associated with grade 3 and 4 pressure ulcers. Cerebral neuropathic pain (multiple sclerosis). Type I and II complex regional pain syndrome.
NOT INDICATED	
Primary headaches (scientific evidence)[21-23]. Fibromyalgia (scientific evidence)[24-28]●. Pain associated with visceral functional disorders (IBS, IBD)[29-32]. Chronic pancreatitis (scientific evidence)[33]◆. Chronic pain as the main symptom of psychiatric disorders (depression, somatic symptom disorder, generalized anxiety disorder, posttraumatic stress disorder). Misuse, abuse, or addiction to opioid analgesics (present or past). Major depressive disorder or suicidal tendencies.	

* Opioid analgesics are one of the different treatment options available.

■ When significant pain or functional improvement has been achieved in the first 4-6 weeks without major adverse effects, the treatment can be continued in the long-term.

● Tramadol, alone or in combination, can be used for no longer than 4-12 weeks.

◆ Opioids must not be used for longer than 4 weeks.

Finally, the main contraindications of analgesic opioids include[13]:

- Hypersensitivity to opioids.
- History of serious adverse effects or lack of response to other previous opioid treatments.
- Severe respiratory disease (respiratory depression, chronic obstructive pulmonary disease, bronchial asthma).
- Gastrointestinal obstruction.
- Severe liver dysfunction.
- Head trauma or intracranial hypertension.
- Seizure disorders.
- Uncontrolled acute psychiatric disorder or risk of suicide.
- Uncontrolled alcohol or drug use disorder.
- Patients under treatment with MAOIs.
- Acute intoxication with alcohol, hypnotics, analgesics with effects on the central nervous system, or other psychotropics
- Inappropriate use of other drugs.
- Pregnancy or breastfeeding.

Adverse effects, medical complications, and risks

The data sheets of the different products containing opioids clearly define the most frequent adverse effects of these drugs[13]:

- Gastrointestinal effects (nausea, vomiting, constipation, decreased appetite, dyspepsia).
- Respiratory effects (bronchospasm, respiratory depression, decreased cough reflex).
- Cognitive effects (confusion, dizziness, thought and attention disorders).
- Sleep disorders (drowsiness, insomnia).
- Other effects (dry mouth, rash, hyperhidrosis, pruritus, asthenia, anxiety, depression, headache, tremor, sexual dysfunction, diarrhea, ataxia, edema, urinary retention, restless legs).

Apart from these adverse effects, it is essential to inform patients about:

- Potential medical complications that may occur with the long-term use of opioids, including neuroendocrine disorders (hypogonadism, amenorrhea, erectile dysfunction), sleep apnea (central apnea or worsening of obstructive apnea), cognitive disorders (memory, concentration, reasoning and executive function), falls and fractures, immunosuppression, and infections[34].

- Other potential risks of opioids that patients are rarely informed about. These are probably less known and sometimes are diagnosed inadequately, but it is crucial to take them into account because, mainly due to the high prescription of these drugs, long-term and high-dose regimens are increasingly frequent:

  » Neurotoxicity[35-37] (opioid-induced neurotoxicity syndrome,[38-47] opioid-induced hyperalgesia[48-57], serotoninergic syndrome[7,8,58-62], central nervous sensitisation[63-73]).

  » Tolerance, physical dependence, and withdrawal syndrome, as predictable effects after repeated administration of opioids (even under prescription), and abuse or addiction, as unpredictable and undesirable effects of treatment with opioids[74-84].

  » Overdose of prescription opioids[85,86].

When a patient does not respond to opioid analgesics, it is crucial to be aware of the associated risks and include them in differential diagnosis, which must go beyond disease progression, development of tolerance and physical dependence on opioids, or the consideration that pain is being undertreated.

Key points for a safe prescription of opioid analgesics

Table 6 shows the rationale for the contents of this report, which will help achieve the safer use of opioid drugs in the treatment of a complex and difficult-to-manage disorder: chronic pain.

Based on these key issues and main recommendations of the most recent published guidelines[15,17,57], we have developed algorithms for each stage of the treatment with opioids for CNCP, which may be useful for clinical decision-making.

What should be assessed before considering the prescription of opioid analgesics?

In a patient with pain, especially in the case of CNCP, aside from pain assessment (Annex I), other aspects need to be evaluated:

- Assessment of functionality and quality of life (Annex I).

- Assessment of previous treatments (type, adherence, effectiveness).

- Assessment of risk associated with the use of opioids: Opioid Risk Tool (ORT)[98,99] (Annex II) and stratification of risk[57] (Annex III).

- Assessment of the risk of overdose at the start of the treatment[57] (Annex IV).

Once these aspects have been assessed appropriately, if opioid analgesia is being considered, the following actions are essential (yet frequently ignored in daily clinical practice despite official recommendations and guidelines):

- To establish objectives for opioid treatment with the patient and with reasonable goals. The objective must not be the eradication of pain (i.e. it is chronic), but rather its relief and improvement of functionality.

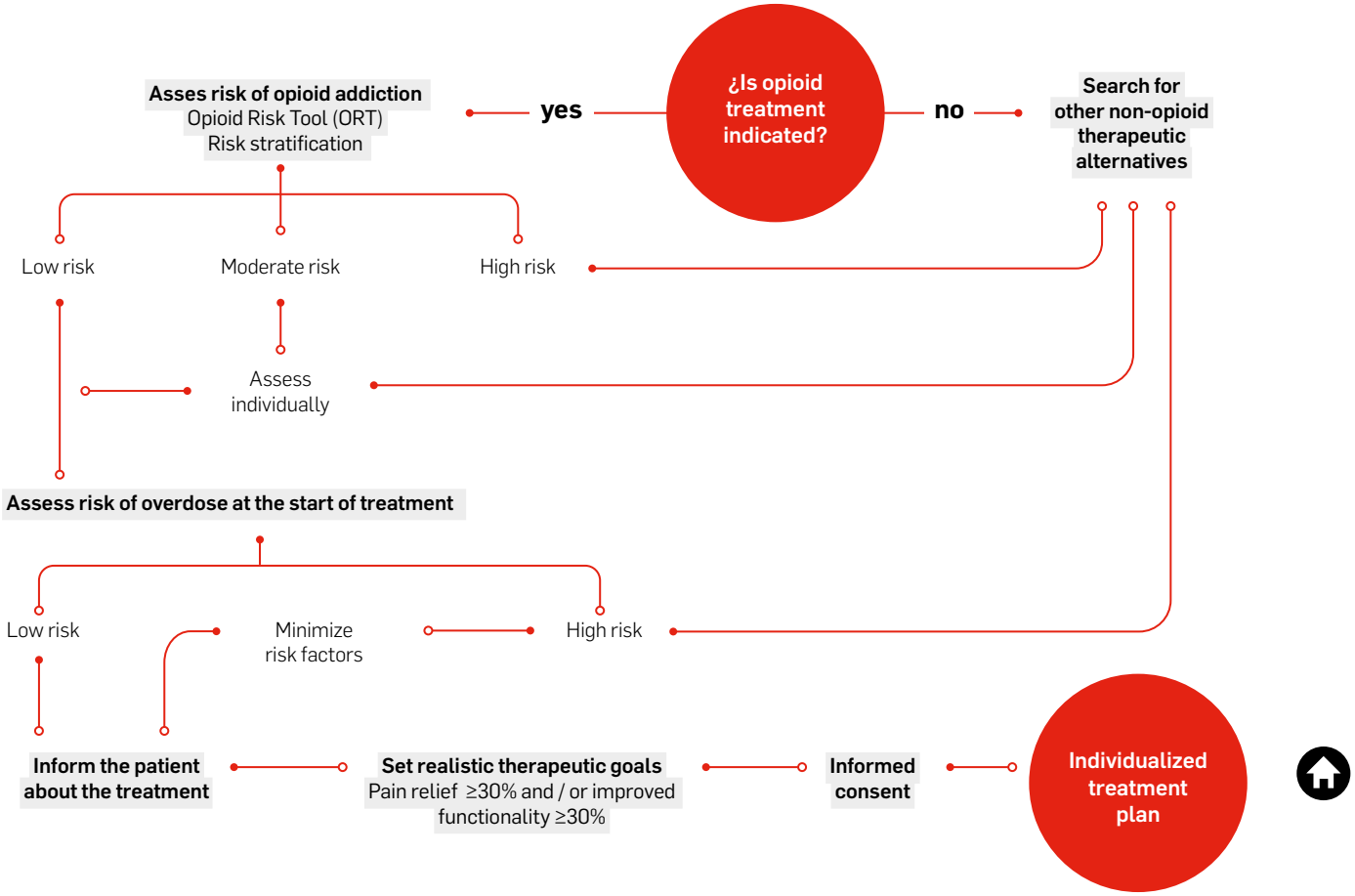
- To give full and realistic information to the patient and their family about all aspects related to treatment with opioids, including risk of overdose, abuse, addiction, and opioid-induced hyperalgesia (Annex V).

- To obtain informed consent from the patient to receive the treatment after being adequately informed (Annex VI).

Table 6. Key points for a safe prescription of opioid analgesics in CNCP.

Throughout treatment, pain management must always be individualized, integrated, multidisciplinary, and structured.[87]
From the start of treatment, the strong emotional element present in chronic pain must be taken into account and appropriately managed (otherwise, the risk of perpetuating pain and impairment increases).[88,89]
A comprehensive clinical assessment must be performed (pain, functionality, and quality of life).[90-92]
Opioid analgesics are not first-line drugs for the treatment of chronic pain (nociceptive or neuropathic).[3,14,15,17]
Opioids are not indicated in neuropathic pain, except tramadol (third line). Tapentadol seems to show some efficacy in diabetic neuropathy, and in back pain with an associated neuropathic component, in regimens for up to two years, but it is potentially addictive.[57]
Treatment with opioid analgesics should only be considered in patients with moderate/severe nociceptive pain when the following circumstances are present: · Expectations for short-term resolution of the main cause of pain. · Confirmed failure of all non-opioid treatments possible (including minimally invasive techniques).
Only a small proportion of patients with CNCP will benefit from the treatment with opioids, and its effectiveness for longer than 3 months is not clearly established.[17,20,93,94]
The WHO analgesic ladder must always be followed, with a progressive approach.[95]
Opioids must play a secondary role in the treatment regimen as the chronicity and complexity of pain increase and the age of the patient decreases.[3,96,97]
In patients with psychiatric disorders, history of drug abuse or misuse of other drugs, treatment with opioid analgesics will be only considered if such conditions are stable, the risks outweigh the benefits, and close monitoring of the patient can be guaranteed15,57
Long-term and high-dose treatments increase the risk of overdose and addiction.[17,57,76]
Concomitant use of benzodiazepines, alcohol or other depressants of the central nervous system increase the risk of overdose.[57,76]
Dose adjustment should be preferably carried out with immediate-release formulations (lower risk of overdose), transitioning to extended-release formulations (lower risk of addiction) once the minimum effective dose has been reached.[17,57,94]
If an opioid at moderate doses is not effective, rotation to another opioid or withdrawal is indicated. In no case should the dose be increased to unacceptable levels or other opioids be added through the same or different route of administration.[57]
Regular follow-up visits should be conducted in all patients for whom opioids are prescribed, and the convenience of continuing or not the treatment should always be evaluated.[14,94]

Algorithm 3. Before starting opioid treatment.



What should be known when prescribing opioids for the first time?

When opioids are prescribed, especially if the patient has never taken them (naive patient), precautions and specific considerations need to be taken into account:

- Starting dose adjustment must be slow and progressive, preferably using immediate-release opioids because starting adjustments with extended-release opioids have a higher risk of overdose[17,57,94].

- Once the minimum effective dose has been reached, a transition is made to extended-release formulations, which have a lower risk of addiction[17,57,94].

- For dose adjustment, oral morphine should remain the standard strong opioid because of its cost-effectiveness and greater experience with its use. If oral administration is not possible, subcutaneous morphine can be used. There is no evidence supporting that a given opioid has higher analgesic effects or is safer than others[20,93,94].

- Avoid using transdermal administration (especially fentanyl patches) for dose adjustment in naive patients, due to the high risk of overdose with the starting treatment[14,15]. It is recommended to start with low doses of immediate-release opioids, and then adjust to reach a dose equivalent to the minimum dose of the patch to be used (12 µg/h of transdermal fentanyl is equivalent to 30 mg/day of oral morphine; and 35 µg/h of transdermal buprenorphine is equivalent to approximately 60 mg/day of oral morphine).

- Titration (or starting dose adjustment) will be considered to have been completed when the minimum effective dose (optimal dose) has been reached. In controlled clinical trials, the average effective dose has been set at 57 mg of MED per day for nociceptive pain, and at 92 mg MED per day for neuropathic pain[3,57,77]. In this regard, it is important to take the following aspects into consideration:

  » If 100 mg MED is exceeded daily, the risk of death doubles. Over 200 mg MED, the risk almost triples[3,77,99-101].

  - » In patients requiring a daily effective dose of more than 50 mg MED, closer follow-up and monitoring of treatment will be needed[15].

- The opioid treatment will be regarded as ineffective –and, thus, withdrawal will be indicated (analgesic de-escalation)– if the patient refers pain after a trial period (6-12 weeks) with adequate follow-up and dose escalation[14,15]:

  - » Insufficient analgesia (pain relief below 30%) and/or low improvement in functionality (functional recovery below 30%).

  - » Unacceptable adverse effects.

  - » Associated medical complications.

  - » Evidence of opioid misuse, abuse or addiction.

How should long-term (> 6 months) follow-up of patients be carried out with opioid analgesics?

Maintenance therapy should be preferably carried out with extended-release opioids (lower risk of addiction)[57,94].

Follow-up visits should take place within periods of no more than three months[17,57,94]. This follow-up would involve a full reassessment of the patient, including at least the following aspects:

- Pain, functionality, and quality of life.

- Compliance with therapeutic guidelines.

- Development of adverse effects.

- Risk of misuse: COMM102 and assessment of potential aberrant behaviors associated with opioids (Table 7)[57]:

  - » With daily doses of more than 50 mg MED, follow-up will be closer[15,17].

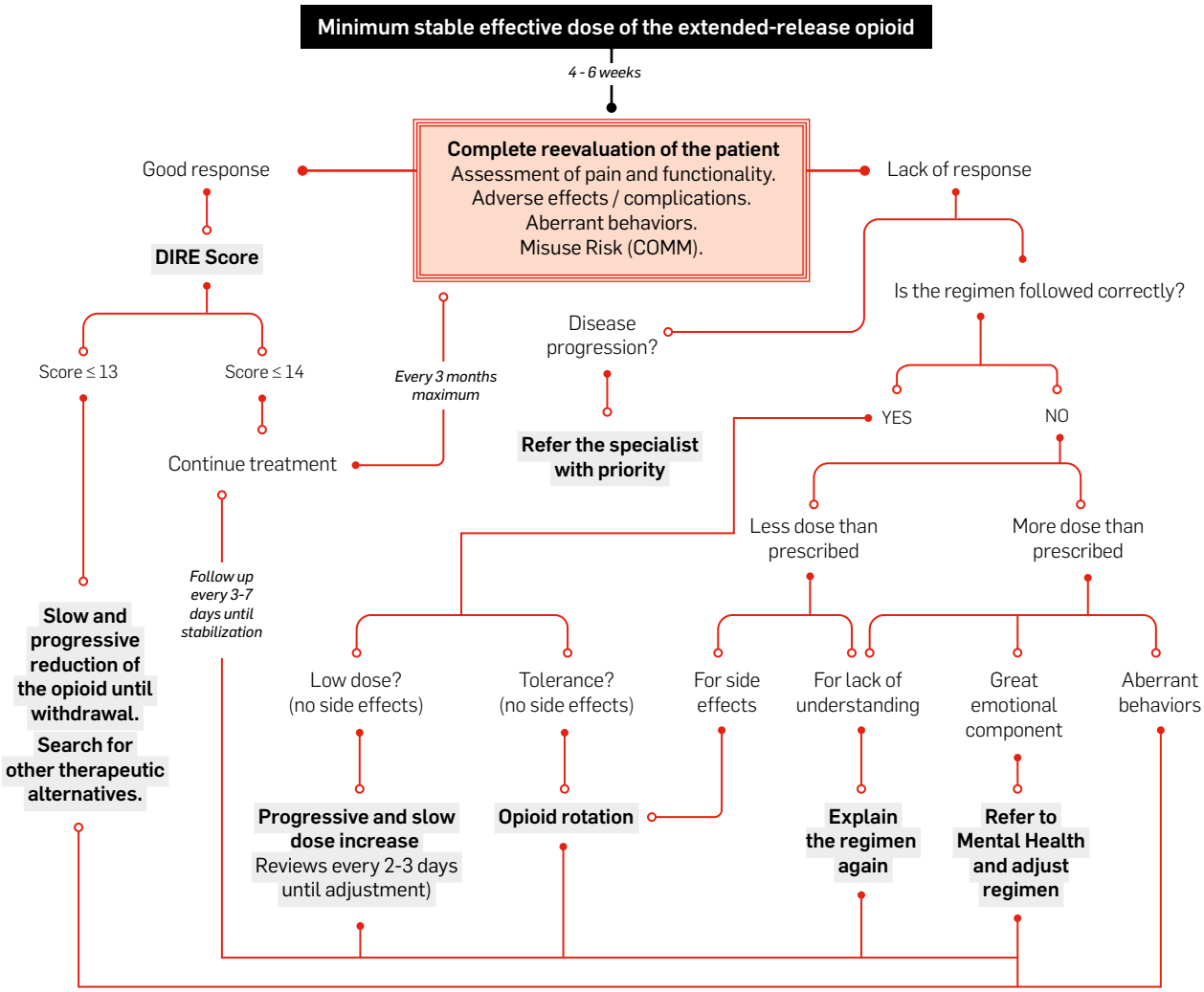
  - » Daily doses of more than 90 mg MED (evidence of higher risk of overdose and addiction) should be clearly justified in the clinical record, and other therapeutic approaches should be considered[14,15,17].

  - » In all patients with CNCP taking daily doses of more than 90 mg MED for a period longer than 6-12 months, it is recommended to try reducing the dose, even withdrawing it to check if it is still effective[14,15]. It is important to inform the patient about the reasons for the decision to reduce the dose of opioids (Annex VII).

Table 7. Aberrant behaviors and alarm signals suggesting misuse of opioid analgesics.

Alteration of the route of administration	Chewing or heating patches. Injecting crushed tablets.
Access to opioids by different routes	Accepting opioids from friends or relatives. Acquiring the drug on the street. Obtaining prescriptions from various doctors. Going frequently to an emergency room to request the drug.
Misuse	Multiple dose increases without medical supervision. Compulsive use instead of following the programmed regimen.
Compulsive search for opioids	Repeated queries alleging lost prescriptions. Requesting (even aggressively) frequent dose increases. Misconceptions about opioid treatment ("Nothing else works"). Reluctance to opioid rotation or dose reduction. Systematically rejecting non-opioid and non-pharmacological treatments.
Repeated withdrawal symptoms	Dysphoria, myalgia, gastrointestinal symptoms, anxiety, compulsive desire to use opioids.
Concomitant disorders	Addiction or harmful use of alcohol or other drugs. Underlying mood or anxiety disorders that do not respond to usual treatments.
Social and family problems	Social deterioration or isolation. Concern expressed by relatives.
Thoughts on opioids	Considering being addicted to or abusing opioids. Admitting using opioids to stabilize their mood. Recognizing withdrawal symptoms.

Algorithm 4. Follow-up and monitoring of opioid treatment.



» The use of daily doses of more than 120 mg MED is never justified. If these doses are required for CNCP control, a referral to the reference pain unit is indicated.

» The use of two or more strong opioids together is not recommended[57]. If a full-dose opioid is not effective, consider an opioid rotation (Table 8)[57].

» In addition to non-response (in terms of analgesia and/or functionality), rotation to another opioid is also indicated in the following cases:

◊ Refractory pain (pain intensity remains above 4 points on the VAS scale despite dose increases).

◊ Development of tolerance requiring such high doses of opioids that administration is impractical, although no toxicity appears.

◊ Presence of neurotoxicity or other significant side effects.

◊ High cost of treatment (socio-health measures).

» If, despite all of this, the patient reports severe and persistent pain that does not respond to escalating doses of the opioid –in addition to potential disease progression, development of tolerance and potential withdrawal through underdose–, other options should be considered[77]:

◊ Failure of opioid treatment.
◊ Development of opioid-induced hyperalgesia.
◊ Abuse or addiction to the prescribed opioid.

Table 8. Opioid rotation process[57].

Step 1	Calculate the morphine equivalent dose (MED) corresponding to the opioid that the patient is taking (opioid A).
Step 2	Calculate the dose of the new opioid (opioid B) corresponding to the morphine dose calculated in step 1, using the conversion factors shown in Table 4
Step 3	Reduce the dose of opioid B calculated in step 2 by 25-75% (safety margin*).
Step 4	Administer for 3-7 days: 70% of the dose of opioid A + 30% of the dose of opioid B calculated in step 3.
Step 5	Administer for another 3-7 days: 30% of the dose of opioid A + 70% of the dose of opioid B calculated in step 3.
Step 6	From day 7-15, administer 100% of the dose of opioid B calculated in step 3.

(*) Safety margin: If the dose of the previous opioid (opioid A) was high (≥ 75 mg MED), the dose of the new opioid is recommended to be 25-50% of the dose of opioid A, converted to morphine equivalents. If the dose of the previous opioid (opioid A) was moderate or low (< 75 mg MED), the dose of the new opioid is recommended to be 60-75% of the dose of opioid A, converted to morphine equivalents. The conversion of any opioid to methadone always requires a 75-90% reduction in the dose of the previous opioid, converted to morphine equivalents.

How should a patient who uses opioids chronically (≥ 6-12 months) and/or at high doses be managed?

Slow and progressive withdrawal of the opioid is indicated in all patients on chronic opioid treatment. Accordingly, some studies suggest that withdrawal of these drugs reduces the intensity of perceived pain and improves mood in patients with severe pain who have been taking opioids for a long time and/or at high doses[17,77].

The rate and duration of dose reduction should be adjusted to patient's response in order to minimize withdrawal symptoms. In general, it is recommended to reduce the starting dose by 5-10% every 1-2 weeks or by 25% every 3-4 weeks. When a third of the starting dose is reached, reduction should be slower[14,15].

Generally, complete withdrawal of the opioid can be done in a period of 2 weeks to 4 months.[14,15] If treatment time is longer, or in case the patient has a cardiorespiratory disease, opioid abuse/addiction or is simply afraid of withdrawal, the dose reduction should be slowed down.

During the process of withdrawal of an opioid, it is advisable to:

- Avoid the use of benzodiazepines as much as possible.
- Maximize pain management with non-opioid treatments and non-pharmacological therapies.
- Have adequate psychosocial support.
- Patients in whom dose reduction is complicated can benefit from coordinated multidisciplinary programs (primary care, pain unit, physiotherapy, occupational therapy, psychology, psychiatry)[14,15].

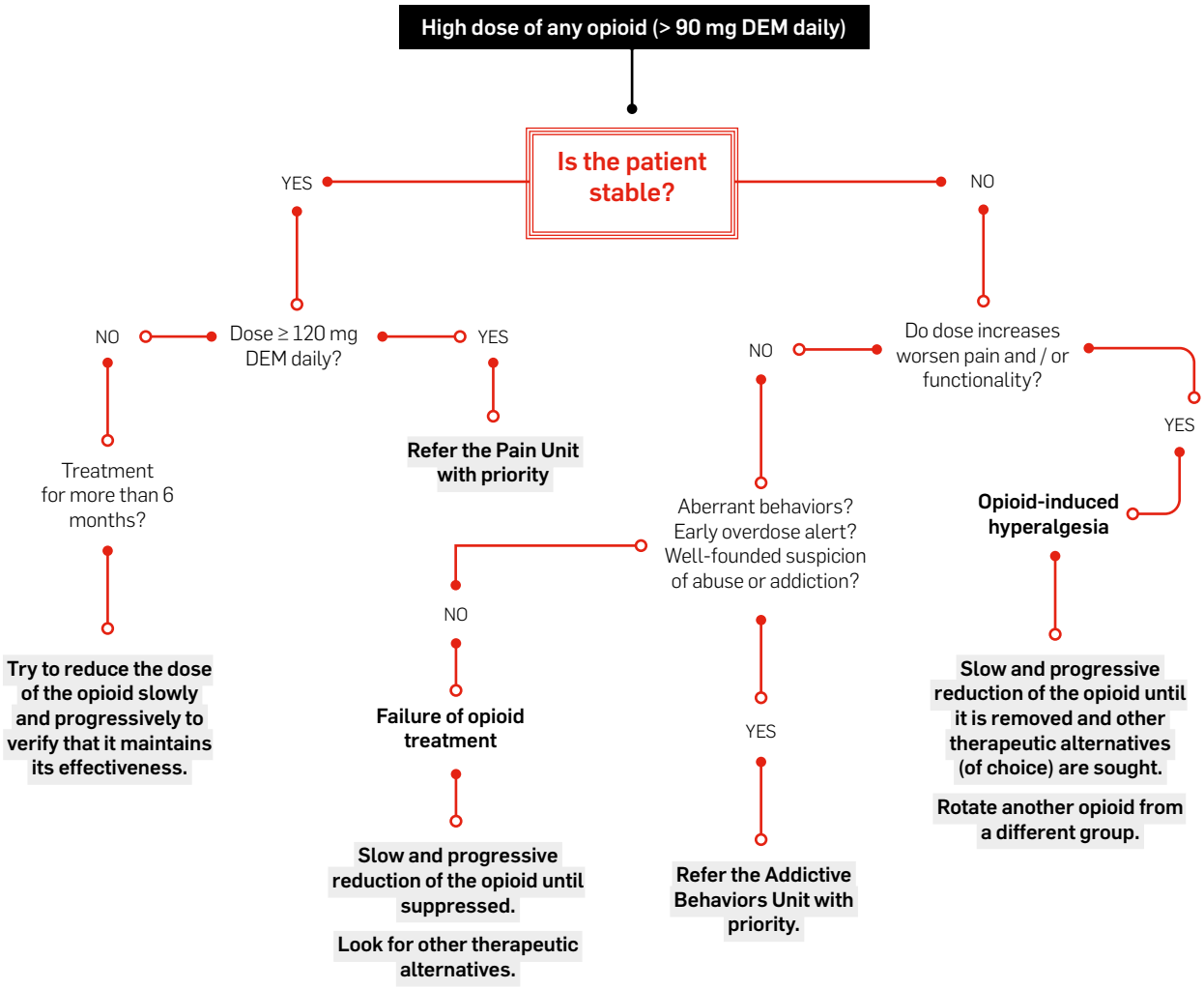
The most appropriate place for the management of patients with abuse or addiction to opioid analgesics should be specific addiction care units.

When is it appropriate to stop opioid treatment?[14,15,17,57,77]

- When the patient requests it.
- When the cause of pain is resolved.
- When there is no clinically significant improvement in pain and/or function.
- When a daily dose of more than 50 mg MED is used without a clear benefit.
- When benzodiazepines or alcohol are used concomitantly.
- When there is suspicion or clear signs of drug use disorders.
- When there is well-founded suspicion or certainty of problems related to the use of opioid analgesics or difficulty in controlling their use.
- When there are early warning signs of overdose (e.g. confusion, sedation, slow and slurred speech).
- When an episode of acute intoxication (overdose) or other serious and intolerable adverse effects occur.

In all these cases, dose reduction should be carried out as mentioned in point 4 above.

Algorithm 5. Management of patients on high-dose and long-term treatment.



Management of transmucosal fentanyl

Preparations with fentanyl citrate or transmucosal fentanyl (TMF) have been marketed in Spain since 2001, in formulations for oral and intranasal administration (sublingual tablets, oral solid forms with applicator, oral film, nasal spray).

Fentanyl is very lipophilic and is rapidly absorbed through the mucous membranes (oral or nasal), and more slowly through the digestive tract. The quick transmucosal absorption, along with the absence of the first-step effect, makes these formulations widely used for breakthrough pain peaks in cancer patients.

Because of this, TMF-containing drugs are only indicated for the treatment of breakthrough pain in adult cancer patients who are already receiving maintenance treatment with opioids to treat chronic cancer pain, as noted in the data sheet of these drugs[13]. Therefore, these formulations should not be used as the first choice for any type of pain, nor should they be used in patients who have never taken other opioids.

What is breakthrough pain?

This term defines a sudden and transient exacerbation of pain, of high intensity (VAS > 7) and short duration (less than 20-30 minutes), appearing on the basis of stable persistent pain, which most of the day is reduced to a tolerable level (VAS < 5) by the fundamental use of strong opioids as maintenance therapy[103].

A patient is considered to be on opioid maintenance therapy when they take at least 60 mg of oral morphine/day, at least 25 mg of transdermal fentanyl/hour, at least 30 mg of oxycodone/day, at least 8 mg of oral hydromorphone/day, or an equianalgesic dose of another opioid for one week or more.

In principle, as some authors point out[104], TMF formulations are most suitable for breakthrough pain, since their profile mimics the time-intensity curve of this type of pain (high analgesic power and short action). However, these two characteristics of TMF constitute a very dangerous double-edged sword, especially when used in patients with CNCP and even in non-terminal cancer patients[57].

What are the risks of administering TMF to non-cancer patients?

Non-cancer patients should not be administered TMF for the following reasons:

- The average dose of opioids for chronic non-cancer pain is already quite high (around 90 mg MED).
- The quick effect of TMF places patients who use it for more than 3-7 days at a higher risk for intolerance, dose escalation, and abuse or addiction[57], unless strict control of its benefits can be carried out.

In February 2018, the Spanish Agency of Medicines and Medical Devices (AEMPS) echoed the inappropriate use of drugs containing TMF outside their indication, since it was generating serious problems due to the associated risk of abuse and dependency[105]. In its information note, the AEMPS makes the following recommendations to healthcare professionals:

- To respect the conditions for authorization of immediate-release forms of fentanyl, for which the authorized indication is breakthrough pain of cancer origin treated with a background opioid analgesic.
- To assess the need for treatment and the use of other therapeutic alternatives in patients already on immediate-release fentanyl treatment for non-cancer pain. These patients can be evaluated for their potential for abuse according to the available questionnaires, and should be adequately informed of the risk of abuse and dependence associated with their use.

When should TMF not be used?

- In patients with any type of non-cancer pain.
- In patients under the age of 18.
- In patients for whom TMF is contraindicated (simultaneous use of monoamine oxidase inhibitors or within 2 weeks after the end of their use, severe respiratory depression, severe obstructive pulmonary disease).
- In patients who have TMF regimens in monotherapy (without background opioid). In these cases, a complete assessment of pain management is indicated, a background opioid is prescribed, and TMF is discontinued if necessary.

For the mitigation of peak pain exacerbations in patients with CNCP, there are several immediate-release alternatives, such as morphine, oxycodone, and buprenorphine (the latter, being a partial agonist, should only be administered in patients using TMF in monotherapy). Selection will be based on the risk of addiction (oxycodone > morphine > buprenorphine), the need for quick relief, the severity and the nature of pain (oxycodone > morphine > buprenorphine).

If the patient was not prescribed a background opioid, once stabilization has been achieved with the immediate-release alternative selected, it is possible to switch to extended-release formulations.

If, in spite of all the above, it is decided to prescribe TMF to a patient with CNCP, what would be the most advisable thing to do?

If it is decided to start or continue treatment with TMF in a patient with CNCP, despite the lack of indication and the legal consequences that this may entail in the event of alleged harm to the patient, it is recommended that informed consent be obtained for the use of drugs that are not authorized in the fact sheet[106], in accordance with the Spanish Royal Decree 1015/2009 of 19 June, which regulates the availability of drugs in special situations.

Final considerations

There is no doubt that opioid analgesics, when used appropriately, are very useful drugs that have relieved the suffering of many patients. However, they are not drugs that should be prescribed to treat chronic diseases, for long periods of time and at very high doses. Neither their action mechanism, nor their objective when marketed, are focused on that purpose.

Currently, there is no strong evidence to support the analgesic efficacy or functional recovery of patients who have long-term opioid regimens for CNCP. Population studies reveal this lack of long-term analgesic efficacy and highlight safety problems and increased adverse effects, especially with the use of high doses (> 100 mg MED per day)[107].

What we have learned so far from the scientific evidence and the clinical data available is that[107]:

- Opioid analgesic efficacy decreases with continued use (by development of tolerance and physical dependence).

- Applying the principles of cancer pain palliative care treatment to the management of CNCP has led to the use of very high doses, which are unsafe and ineffective.

- Chronic pain should be considered as a response to stress involving the endogenous opioid system (reward system, and cerebral limbic and cortical areas). Therefore, people with complex chronic pain that is refractory to usual treatments are at high risk of abuse.

- Those patients who report the highest need for opioids are usually those who have the worst outcome from treatment, not only in terms of pain mitigation, but also in terms of increased risk of misuse, abuse, and death.

Far from taking all of the above into account, opioid prescription has increased in recent years, sometimes indiscriminately and without adequate follow-up of patients. This is becoming a public health problem, not only in the United States, but also in many other parts of the world[108,109]. The opioid analgesics most involved in this conflict are tramadol and fentanyl, precisely the two active principles whose use has been most widespread in clinical practice[2].

We should therefore start thinking that opioid treatment for chronic pain should be the exception, rather than the rule. Their use should be limited to the minimum period of time possible, with the lowest effective dose, assessing whether it is effective and well tolerated by the patient.

Conclusions

It is crucial that prescribers have the right tools to know whether opioids can be a valid and safe alternative, always bearing in mind the following points[110]:

Opioids are very effective drugs for acute pain and for pain at the end of life, but the evidence for their long-term usefulness in chronic pain is limited.

A small percentage of patients can achieve adequate pain mitigation with long-term opioid use, provided that they can be kept at low doses, and especially if their use is intermittent. Nevertheless, it is difficult to identify at the start of treatment which patients would be suitable for long-term therapy.

The risk of damage increases considerably with daily doses of more than 120 mg MED without providing a greater benefit, so it would be indicated to reduce the dose or suspend opioid treatment in a planned and multidisciplinary way.

If pain is still severe after opioid treatment, the patient must be told that treatment is not working and must be stopped. Accepting that opioid treatment may fail is the first step to improving opioid use.

Chronic pain is a very complex pathology. If patients have refractory and debilitating symptoms, despite the use of high doses of opioids, a detailed evaluation of the many emotional influences that may be intervening in their pain experience in essential.

ANNEX I
ASSESSMENT OF PAIN, FUNCTIONALITY AND QUALITY OF LIFE

Type of pain	☐ Nociceptive	☐ Neuropathic (DN4)	☐ Mixed		
Location	☐ Focal	☐ Multifocal	☐ Diffuse		
	☐ Superficial	☐ Deep			
	☐ Localized	☐ Irradiated	☐ Referred		
Intensity	 0 = No pain | 1-3 = Mild pain | 4-7 = Moderate pain | 8-10 = Severe pain				
Time characteristics	Start, duration, course and pattern				
Aggravating factors					
Relieving factors					
Functionality / quality of life	☐ BPI-SF	☐ IDF	☐ PCS	☐ GADS	☐ HADS
	☐ Duke-Unc	☐ Oviedo			
Potential OIH (opioid-induced hyperalgesia)	☐ Yes	☐ No			

DN4 Douleur Neuropathique 4
BPI-SF Brief Pain Inventory – Short Form
IDF Inventory of Deterioration and Functionality
PCS Pain Catastrophizing Scale
GADS Goldberg Anxiety and Depression Scale
HADS Hospital Anxiety and Depression Scale
Duke-UNC Functional social support questionnaire
Oviedo Sleep quality questionnaire

All these questionnaires are available at: www.analgesicosopioides.org

ANNEX II
OPIOID RISK TOOL

		Women	Men
Family history of substance abuse	Alcohol Illegal drugs Prescription drugs	1 2 4	3 3 4
Personal history of substance abuse	Alcohol Illegal drugs Prescription drugs	3 4 5	3 4 5
Age (check if age is between 16 and 45)		1	1
History of sexual abuse		3	0
Psychiatric disorder	Attention deficit Obsessive compulsive disorder Bipolar disorder Schizophrenia Depression	2 1	2 1
	Total score		

1 – 3 Low risk.

4 – 7 Moderate risk: opioid analgesics may be used with careful monitoring and adequate follow-up of the patient.

≥ 8 High risk: in this case, if possible, avoid the use of opioid analgesics.

ANEXO III
RISK STRATIFICATION

	Low risk	Medium risk	High risk
Pain	Localized	In less than three areas	Diffuse
Objective signs and symptoms	Present	Present	Absent
Pain exacerbations	Absent	Infrequent	Frequent
Psychiatric comorbidity	Absent or mild	Moderate and controlled	Severe or uncontrolled
Organic disorders	Absent or mild	Moderate and controlled	Severe or uncontrolled
Family history of addiction	No	Controlled	Active consumption
Personal history of addiction	No	Controlled	Active consumption
Tolerance	Absent	Mild	Significant
Physical dependence	Absent	Absent	Present
Hyperalgesia	Absent	Absent	Present
Abuse	Absent	Absent	Present
Level of pain acceptance	High	Moderate	Low
Coping strategies	Adaptive	Adaptive or unadaptive	Unadaptive
Functionality	Functional or quasi-functional	Dysfunctional with attempts at normalization	Clearly dysfunctional
Acceptance of multimodal treatments	Yes	Yes	No

ANNEX IV
ASSESSMENT OF THE RISK OF OVERDOSE AT THE START OF TREATMENT

Patient factors	Physician factors	Opioid factors
☐ Elderly. ☐ Regular consumption of benzodiazepines or alcohol. ☐ Kidney failure. ☐ Liver failure. ☐ COPD. ☐ Sleep apnea. ☐ Cognitive impairment.	☐ Incomplete assessment. ☐ Dose adjustment done too quickly. ☐ Combination of opioids and other sedative drugs. ☐ Failure in dose monitoring. ☐ Insufficient information given to the patient and/or family.	☐ Codeine and tramadol (lower risk). ☐ Extended-release formulations (higher risk).

ANNEX V
MODEL OF INFORMATION SHEET FOR PATIENTS AND THEIR FAMILIES

What are opioid analgesics?

Opioid analgesics are a group of drugs used to relieve severe pain, along with other drugs and non-drug therapies.

What are they used for?

The main goal of this treatment is to reduce pain as much as possible and improve your functionality (your ability to be more active). Your function may improve despite the pain, which may not go away completely.

You, your doctor and your nurse will make sure that the medication helps you achieve your goals (to be more active and decrease pain).

Your doctor and nurse will see you in the office on several occasions to adjust the dose and assess pain relief, your ability to reach your goals and the occurrence of any adverse effect.

What adverse effects can occur if you take opioids?

Like any medication, opioids can cause undesirable effects. The most common are nausea, vomiting, constipation, drowsiness, dry mouth or skin, and itchy skin. If they occur, tell your doctor or nurse and they will help to lessen these effects.

Opioids are drugs that act on your brain, so they also have the ability to cause tolerance (the need for increasing the dose to get the same effect with continued use) and physical dependence, which is responsible for the appearance of a withdrawal syndrome if you stop taking opioid medication on your own abruptly.

Opioid withdrawal syndrome is not dangerous, but it can be very unpleasant. Withdrawal symptoms are similar to those of the flu (runny nose, joint and muscle aches, chills, fever), along with yawning, dilated pupils, nausea, diarrhea, and irritability.

If you experience withdrawal symptoms, it does not mean that you have become addicted, just that you have stopped the medication too abruptly. If you wish, your doctor will guide you to stop the medication slowly enough so that you do not suffer this withdrawal reaction.

In the event of withdrawal, you will also experience increased sensitivity to pain, which is known as hyperalgesia. Paradoxically, however, this hyperalgesia is sometimes caused by the continued use of opioids without withdrawal, in which case you should consult your doctor or nurse.

Overdose of opioid analgesics

Overdose of opioid analgesics is rare, but you and your family should be able to recognize their signs.

Overdose slows down thinking and breathing. This could lead to brain damage, trauma, and even death.

Combining the use of opioid analgesics along with the consumption of alcoholic drinks or sleeping pills greatly increases the risk of overdose.

You should call your doctor or nurse (or the emergency room if your healthcare facility is closed) if you notice any of the following signs of overdose: slow and slurred speech, getting upset or yelling easily, difficulty keeping your balance, falling asleep in the middle of a conversation or activity.

Addiction to opioid analgesics

Addiction to opioid analgesics is a chronic disease in itself that occurs when a person uses the drug for reasons other than those prescribed by their doctor and/or when they cannot control the urge to take the drug, increasing the prescribed dose on their own.

Although the risk of addiction to opioid drugs is not very high, some patients are at greater risk of developing addiction (especially if they have a history of alcohol or other drug addiction, or if they suffer from psychiatric disorders). No patient is immune to addiction.

The medication your doctor has prescribed is only for you and can be very dangerous for others

The dose is adjusted to your body and can be very dangerous for other people. You have reached the dose slowly, but someone who is not used to this medication could experience a serious reaction, and even die.

You should not give your medication to anyone – it is illegal and may harm or kill someone.

You should store your medication safely at home (preferably in a locked place). The medicine cabinet in the bathroom is not a safe place, as research shows that other people, particularly teenagers, may take them to use them or offer them to others. Be especially careful if there are children in the house or if you have pets – do not leave this medication within reach.

Final recommendations

Opioid analgesics have risks, but they can be controlled if you work in cooperation with your doctor and nurse.

Take the medication as prescribed by your doctor. The use of high doses of opioids is associated with higher risk of addiction, respiratory depression, and death.

Do not drive or operate machinery at the start of treatment, during a period of gradual increase in dose, or if the medication makes you feel drowsy or confused.

Only your doctor should prescribe your analgesic medication. It is not safe to get it from two different doctors.

You should not take opioid analgesics from another person, and you should not share your medications with others.

Your doctor will provide you the prescriptions you need until your next visit. Please, keep your prescriptions safe. If you use up your medication too quickly or lose a prescription, your doctor may not be able to write another one. Please, be aware of this.

If you cannot follow these indications, opioid analgesics may not be safe for you, so your doctor will not prescribe them.

ANNEX VI
MODEL OF INFORMED CONSENT FOR TREATMENT WITH OPIOID ANALGESICS

PATIENT´S IDENTIFICATION DATA

Date: _____

Mr./Ms.: _____

con ID no.: _____

I DECLARE:

That I have been informed about what opioid analgesics are, what they are used for and what the benefits of taking these drugs are in my case, as well as what potential side effects may occur (including tolerance, withdrawal, overdose, addiction, and increased pain).

That I have been instructed on my treatment plan, including instructions for the correct use of these medications, and warning and alarm signs to be aware of in order to reduce the risks associated with the use of opioids.

That I have understood all the information and have been able to ask all the questions I have considered relevant about my treatment plan, obtaining the appropriate answers.

That I have been recommended a reflection period of at least 24 hours before accepting the agreed treatment plan, being able to refuse to initiate it if I consider it appropriate.

☐YES / ☐NO I freely AUTHORIZE AND CONSENT

to the initiation of the proposed procedure, which includes treatment with opioid analgesics to try to achieve an improvement in pain and functionality, knowing and assuming the potential risk of complications or adverse effects that may appear throughout my treatment with these medications, as I have been specifically informed.

I hereby freely sign this informed consent document, having read and verified it.

SIGNATURE OF THE PATIENT / LEGAL REPRESENTATIVE

SIGNATURE OF THE DOCTOR AND MEMBER NO.

ANNEX VII
MODEL OF INFORMATION SHEET FOR PATIENTS PRIOR TO REDUCTION/SUPPRESSION OF OPIOID ANALGESICS

Why are you advised to reduce/suppress opioid treatment?

- High doses of opioids over a long period of time may not provide good pain relief because of the development of tolerance.
- Even opioids may be making the pain worse by the development of opioid-induced hyperalgesia.
- Many of the side effects increase with high doses and with prolonged treatment.

Opioids may not be helping you as much as you think. Decreasing the dose, even to the point of suppressing the drug, may improve your pain, your mood, your function, and your quality of life.

What are the side effects of long-term opioid treatment?

- Tolerance, physical dependence, and withdrawal syndrome.
- Constipation and intestinal obstruction.
- Drowsiness (falls and accidents).
- Fatigue, lack of energy, dysfunction, depression (worse quality of life).
- Sleep apnea.
- Decrease in testosterone in men (decreased sexual desire, osteoporosis, lack of energy).
- Decrease in estrogens and progesterone in women (osteoporosis, lack of energy, amenorrhea).
- Opioid-induced hyperalgesia.

If you abruptly decrease or stop the dose of the opioid, you may experience withdrawal symptoms, which are to be expected – they do not mean you are an addict. These are unpleasant symptoms, but they are not life-threatening.

One of the first withdrawal symptoms is increased pain, which will lessen within a few days or weeks after ceasing to take the opioids.

Although pain would improve (only temporarily) if the dose of the opioid was increased, this is not proof that the opioid is working effectively.

What can you experience during the reduction/suppression period of your opioid treatment?

- Pain (general pain, joint pain, muscle pain). The pain associated with withdrawal ceases within 1-2 weeks. Non-opioid analgesics and non-pharmacological therapies are useful.
- Withdrawal symptoms (sweating, chills, goosebumps; headache, muscle aches, joint aches; abdominal cramps, nausea, vomiting, diarrhea; fatigue, anxiety, difficulty sleeping). These symptoms may be very unpleasant, but generally do not pose a life-threatening risk. There are useful drugs to relieve these symptoms. If the opioid is stopped abruptly, the most severe symptoms appear 24-72 hours after the last dose and they decrease in 3-7 days (fatigue and low mood may last longer). With a slow reduction of the opioid, withdrawal symptoms are usually milder.

An increase in pain and dysfunction that is not reduced in 3-4 weeks may not be due to withdrawal and will need to be reassessed by your doctor.

If you do not tolerate withdrawal symptoms, dose reduction can be stopped for a while or a slower reduction can be made, but the dose of the opioid should never be increased again.

How can the reduction/suppression of your opioid treatment be done?

- Method 1: Gradual dose reduction with frequent follow-up by your medical team. This is the method of choice.
- Method 2: Replacement of the opioid you are taking with buprenorphine/naloxone or methadone, and then gradual reduction. This method should preferably be done in an addiction care unit.
- Method 3: Quick dose reduction (within a few days/weeks, or even immediately). This method will preferably be done in a hospital setting, to monitor withdrawal symptoms.

During the reduction/suppression of your opioid treatment, seek the support of family and friends, and learn and practice non-pharmacological strategies for pain management.

Remember that the long-term goal is to relieve pain (chronic pain cannot disappear completely) and, above all, to improve your quality of life.

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