



## **Analgesic opioid use disorders in patients with chronic non-cancer pain: A holistic approach for tailored management**

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1 ANALGESIC OPIOID USE DISORDERS IN PATIENTS WITH CHRONIC NON-CANCER PAIN:  
2 A HOLISTIC APPROACH FOR TAILORED MANAGEMENT

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**Abstract:**

Chronic pain is a major public health issue that frequently leads to analgesic opioid prescriptions. These prescriptions could cause addiction issues in high-risk patients with associated comorbidities, especially those of a psychiatric, addictive, and social nature. Pain management in dependent patients is complex and is yet to be established. By combining the views of professionals from various specialties, we conducted an integrative review on this scope. This methodology synthesizes knowledge and results of significant practical studies to provide a narrative overview of the literature. The main results consisted in first proposing definitions that could allow shared vocabulary among health professionals regardless of their specialties. Next, a discussion was conducted around the main strategies for managing prescription opioid dependence, as well as pain in the context of opioid dependence and associated comorbidities. As a conclusion, we proposed to define the contours of holistic management by outlining the main guidelines for creating a multidisciplinary care framework for multi-comorbid patients with chronic pathologies.

**Keywords:**

chronic pain; drug abuse; overdose; opioid withdrawal; opioid proper use

## 1. INTRODUCTION

The chronic nature of pain makes it a unique pathology regardless of the initial etiology. Acute pain is the response to an essential physiological mechanism which alerts the body when it is at risk of injury. In some patients, this pain may persist, according to various mechanisms (neuropathic, nociplastic or nociceptive), which will be developed later in this manuscript (see part 4). Based on the definition, chronic pain could be defined as experiencing pain for a period exceeding 3-6 months (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011). The global prevalence of chronic pain is estimated at 19%-32% (Breivik et al., 2006; Chenaf et al., 2018; Treede et al., 2015). A recent analysis of the National Health Interview Survey conducted by the Center for Disease Control and Prevention estimated that 1 in 5 adults in the USA has chronic pain (Dahlhamer, 2018). Chronic pain is among the most common reasons for medical visits and frequently leads to opioid analgesic prescriptions (Dahlhamer, 2018; Daubresse et al., 2013; Treede et al., 2015); further, it has become a major public health issue in two ways. First, it has a high annual economic cost in terms of healthcare and lost productivity, which is estimated at \$560-630 billion per year (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011). Second, given the considerable increase in opioid prescription over the past two decades, there has been a concomitant increase in the rates of misuse (21-29%) and addiction (8-12%) in patients with chronic pain (Vowles et al., 2015), which leads to unintentional intoxication and death (Shipton et al., 2018). This trend began in North America before gradually spreading to most of the world's industrialized countries (Agence Nationale de Sécurité du Médicament et des produits de santé, 2019; Chenaf et al., 2016; European Monitoring Centre for Drugs and Drug Addiction, 2018; Gallagher and Galvin, 2018; Häuser et al., 2017; Manchikanti et al., 2018; Van Amsterdam and Van den Brink, 2015) and several developing countries in Africa and Asia (United Nations Office on Drugs and Crime, 2018). Depending on the criteria used, a literature review conducted by Højsted and Sjøgren (2007) reported that the prevalence of prescription opioid problematic behavior in patients with chronic non-cancer pain was up to 50%. Further, this risk is increased among patients with associated comorbidities,

particularly psychiatric and addictive, which are common in patients with chronic pain (Barry et al., 2016; Barth et al., 2013).

These risk factors should be assessed prior to the initial opioid analgesic prescription. Upon initiation of the prescriptions, it is necessary to analyze the relevance of each renewal and to check for potential problematic use of prescribed opioids, as well as the most appropriate pain management.

The first part of this article will attempt to define the terms in favor of a shared vocabulary between health professionals involved in the management of this category of complex patients, regardless of their specialty. The following sections will first outline the withdrawal strategies that may be proposed for the opioid use disorder of these patients, and then the possibilities for analgesic management of their chronic pain, taking into account their potential co-morbidities. The final section will consider a holistic approach for the tailored management of prescription analgesic opioids in patients with chronic pain, with the exclusion of progressive cancer, depending on the different problematic use patterns.

This integrative review provides a narrative overview across various lines of research in order to inform experts and non-experts alike. This methodology allows the synthesis of knowledge and the possibilities of using the results of significant practical studies. It allows the integration of several methods, both qualitative and quantitative. In this regard, an in-depth systematic report of specific research fields is beyond the scope of this work. However, for further reading, we refer throughout this review to systematic or more in-depth work, for each topic addressed.

## **2. DIFFERENT TYPES OF ANALGESIC OPIOID USE DISORDERS**

The diagnosis of opioid use disorder appeared in the 5th version of the *Diagnostic Statistical Manual of Mental Disorders* (DSM), (American Psychiatric Association, 2013; Hasin et al., 2013), and combines the categorical diagnoses of abuse, dependence and addiction from the previous edition, which continue to be used frequently (Substance Abuse and Mental Health Services Administration, 2016). This evolution corresponds to the clinically observed continuum, which focuses not on the

existence of ‘substance addiction’ but on the use made of the substance, of increasing severity - mild, moderate, severe - according to the number of rated clinical criteria.

Some of these diagnoses, established in the absence of chronic pain, lose their meaning when placed in a pain context where the opioid involved in the substance use disorder is prescribed and dispensed through conventional networks (Hasin et al., 2013). Some attempts to define these diagnoses have been published by different academic societies, and show convergences, without reaching a consensus (American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, 2001; O’Connor et al., 2013; Quinlan and Cox, 2017; Savage et al., 2003; Smith et al., 2013; Webster and Fine, 2010). The definitions proposed in this article are not intended to reach a consensus but to summarize the main points of the definitions proposed by these academic societies, enriched by the transdisciplinary vision of the authors’ different specialties - psychiatrists, addictologists, pharmacologists, and pain physicians.

Diagnostic criteria for opioid use disorder have been defined in patients free of chronic pain (American Psychiatric Association, 2013). They are partially unsuitable for patients who have developed a substance use disorder related to opioid analgesics prescribed in the context of chronic pain. For example, the criterion assessing the desire to reduce opioid use may be limited by pain, not by loss of control related to the use disorder. The notion of time spent obtaining the substance is not valid as it is prescribed and dispensed through conventional health care networks, nor are the criteria assessing the impact of opioid use on general activities of daily living that are already impacted by pain and/or adverse treatment effects. Therefore, to differentiate it from the broader concept of opioid use disorders, we will refer to this subtype of use disorder, which focuses on opioid analgesic use in chronic pain, as a prescribed opioid use disorder (POUD). Table 1 summarizes all the definitions used in this manuscript.

## **2.1 Tolerance, pharmacodependence and withdrawal syndrome**

Tolerance is a physiological adaptation mechanism causes patient habituation with subsequent progressive loss of efficacy and a need for increased doses to maintain the expected effect (Quinlan

and Cox, 2017; Webster and Fine, 2010). This adaptation constitutes a new physiological steady state of the central nervous system (Smith et al., 2013). Therefore, a sudden decrease or withdrawal of the drug, as well as an excessively long interval between two drug doses, can lead to balance disruption and lead to a withdrawal syndrome with severe physical and psychological effects, indicating the existence of pharmacological dependence to the substance. (American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, 2001). All opioids have similar symptoms; however, the symptoms vary in terms of severity and duration. Patients might begin experiencing symptoms after 6-30 hours depending on the opioid elimination rate. The main symptoms of opioid withdrawal syndrome include lacrimation; rhinorrhea and sneezing; yawning; hot and cold flushes; sweating and piloerection; craving; anxiety; restlessness and irritability; disturbed sleep; gastrointestinal tract symptoms; muscle, bone, and joint aches and pains; headache; muscle cramps; and tremor. The severity of signs and symptoms can be assessed using validated withdrawal scales, including the Clinical Opiate Withdrawal Scale (Wesson and Ling, 2003).

## **2.2 Problematic use of prescription analgesic opioids**

### **2.2.1 Misuse and abuse**

Misuse is a broad clinical concept referring to all uses other than those for which the drug was prescribed or indicated and without consideration of intentionality or potential consequences. Studies on prescription opioids have widely applied the “misuse” concept as demonstrated by the findings of a recent systematic review (Brady et al., 2016). The definition of misuse is sufficiently broad to encompass most of the aberrant prescribed opioid uses, including individuals who do not meet the criteria for substance use disorder or dependence. Therefore, exploring misuse is simple and suitably allows for large-scale pharmacoepidemiological studies, especially big-data analytics on insurance claims databases (Cochran et al., 2015) or nationwide surveillance databases (Dart et al., 2015). However, there are pitfalls and ambiguity associated with the common definition of misuse. The definition of inappropriate medication use can be based on different criteria, including the characteristics of the user (i.e., non-prescribed use of a prescription-only drug) or the prescription



(i.e., dosage and/or treatment duration), reason for use (e.g., use for recreational purposes, anxiolytic, hypnotic, and stimulant-effect seeking), non-respect with the summary of product characteristics (e.g., use for a non-validated indication or by a non-conventional administration route, such as long-term use of subcutaneous or intravenous morphine), and lack of the clinically relevant symptoms (e.g., lack of pain) (Barrett et al., 2008).

However, some situations in prescribed opioid practice hardly fit these criteria. For example, some off-label opioid prescriptions might not follow the leaflet, particularly the dosage and treatment duration, but are still regarded as medical use as long as the patient follows the prescription. Further, the use of opioid analgesics not prescribed to the individual but obtained from family, friends, or the black market might comply with the summary of product characteristics; however, the lack of prescription qualifies it as misuse since it was not validated by a physician. Finally, it is occasionally difficult to differentiate between misuse and pseudo-addiction in some patients (see part 2.2.3).

However, in clinical practice, “misuse” remains a simple and convenient term that encompasses most of the aberrant use patterns of prescribed drugs, including opioid analgesics.

Moreover, “abuse” occasionally has a similar definition; however, it can cause confusion since the DSM-IV-TR concept of “abuse” is quite different (Substance Abuse and Mental Health Services Administration, 2016). However, this “abuse” concept preferentially refers to non-therapeutic substance use.

## 2.2.2 Addiction

In 2001, an American pain expert consortium proposed the following definition for substance addiction: a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors that influence its development and manifestations. Substance addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, 2001). This definition demonstrates the cardinal addiction features, which are sustained by long-lasting structural and functional

neuroadaptations in the reward, motivational, and emotional brain circuits (Kalivas and Volkow, 2005; Volkow and Morales, 2015).

The concept of craving is a central element in this definition and in addiction assessment. It is characterized by an intense and compulsive desire to use a substance or engage in hedonic behaviors. Craving has been recently identified as a central concept and clinically relevant feature in addictive behavior and is included in the DSM-5 criteria. Laboratory (Carter and Tiffany, 1999; Childress et al., 2008) and daily life studies using ecological momentary assessment approaches have demonstrated a relationship among craving episodes, substance use, and relapse risk (Fatseas et al., 2015; Serre et al., 2015). There is a clear difference between a craving and physical dependence with the latter being related to physiological adaptation to chronic opioid exposure. Conversely, whereas physical signs of withdrawal, or physical tolerance to opioids that the body may have gradually developed, disappear quickly and naturally after opioid abstinence, craving can persist years after opioid discontinuation. This persistence of craving is a relapse risk factor that increases the risk of overdose in a patient who is physically withdrawn from opioids and, thus, has a tolerance that has dissipated. The management, particularly pharmacological, of opioid withdrawal promotes a better control of craving and reduces the risk of relapse and overdose (Kakko et al., 2019; Kreek, 2006).

These notions regarding a patient's loss of control over his/her consumption and having cravings are particularly relevant since they allow discrimination of patients suffering from a real opioid addiction from those only experiencing symptoms of physical and/or psychological dependence.

### 2.2.3 Pseudo-addiction

Pseudo-addiction refers to the aberrant use of prescribed analgesic treatments by a patient with inadequately managed pain. In this context, pseudo-addiction disappears upon the improvement of analgesic management (Greene and Chambers, 2015; Webster and Fine, 2010).

Based on previous definitions, this notion might constitute a language abuse in situations where the patient does not feel a loss of control or associated craving. This suggests that it would then be more appropriate to include definitions for pseudo-misuse or abuse. However, adding terminology would

unnecessarily complicate the subject without any particular benefit since the solution involves improving chronic pain management using pharmacological and non-pharmacological strategies (see part 4).

#### 2.2.4 Opioid-induced hyperalgesia

Hyperalgesia is defined as “increased pain from a stimulus that normally provokes pain” (International Association for the Study of Pain Task Force on Taxonomy, 1994). The iatrogenic phenomenon of opioid-induced hyperalgesia (OIH) is described as “a state of enhanced pain sensitization in patients who are on chronic opioid therapy” (Yi and Prybylowski, 2015).

This paradoxical body reaction could be confused with the tolerance phenomenon since they both involve reduced opioid analgesic response (Hayhurst and Durieux, 2016). However, unlike in tolerance phenomenon, patients with OIH report no or very short-term pain relief upon increased doses. Finally, it is generally associated with a higher pain intensity than that initially reported with generalized, diffuse, and poorly systematized complaints (Lee et al., 2011; Ramasubbu and Gupta, 2011). OIH generally occurs faster than the tolerance phenomenon; further, its pathophysiological mechanism remains unclear (Raffa and Pergolizzi, 2013). There is no consensus on OIH management; however, it mostly involves progressive withdrawal strategies, opioid rotation, use of N-methyl-D-aspartate (NMDA) antagonists, e.g., ketamine, methadone, or dextromethorphan, as well as other non-opioid pharmacological and non-pharmacological strategies (Lee et al., 2011; Ramasubbu and Gupta, 2011; Yi and Prybylowski, 2015).

### 3. DIFFERENT STRATEGIES FOR MANAGING PRESCRIBED OPIOID USE DISORDERS

The concepts defined above (see part 2 and Table 1) show the existence of different types of deviant use of opioids that are prescribed to chronic pain patients for analgesic purposes, grouped under the term “POUD” in this study. POUD management in patients with chronic pain addresses two main concerns; namely, eliminating aberrant behavior that can lead to serious complications and restoring a care framework that allows efficient chronic pain management. Currently, there is no standardized and validated strategy for chronic pain management in patients with POUD. In the absence of validated

recommendations, the different management options should be presented to the patient and applied in a collaborative manner (Dowell et al., 2016). The patient should be informed of the rapid loss of body tolerance to opioids in the days following withdrawal and the resulting increased risk of overdose if opioids are reintroduced at doses similar to those prior to withdrawal (Chang et al., 2018; Dunlap and Cifu, 2016). Prescription of a naloxone rescue kit increases vigilance over this risk and reduces mortality from overdose (Boyer, 2012; Wermeling, 2015).

The key points of opioid prescription in chronic pain patients are outlined in Table 2, according to the temporality of patient management: start of care (before any opioid prescription or in case of active opioid prescriptions), when opioid is prescribed, and after the opioid prescription. The table summarizes the elements to be taken into account when the physician is confronted with a prescription or the renewal of a prescription of opioids for chronic pain.

Prior to management (see Table 2), it is important to carry out a complete history of the disorders and accurately assess the patient's pain complaints. A meticulous interview should be conducted that eliminates the need for an etiological assessment and allows for phenotyping of the prescribed analgesic opioid disorder and assessment for associated psychiatric and addictologic comorbidities. The latter factors might interfere with the patient's management or cause relapse; therefore, they require management. The use of validated POUD screening, e.g., the Prescription Opioid Misuse Index (Knisely et al., 2008); risk-stratification (Webster and Webster, 2005); and comorbidity assessment tools might be relevant for interview completion (Dowell et al., 2016). Therefore, regardless of the short- or long-term pharmacotherapy, it might be appropriate to offer holistic care involving a combination of pain physicians, psychiatrists, addiction physicians, and social workers. Further, it is imperative to combine psychotherapy (motivational and supportive, cognitive and behavioral, etc. see part 4.3.2), physical activity, and social and occupational therapies to allow functional recovery perspective and cost-efficient consultation with the general practitioner (care coordinator) (Fashler et al., 2016; Gatchel and Okifuji, 2006; Guzmán et al., 2001; Stanos, 2012).

### 3.1 Abrupt withdrawal

From a symptomatic approach, pharmacologic management of opioid withdrawal syndrome has been well established in patients with chronic pain without comorbidities and/or prolonged or high-dose opioids (Agency Medical Director's Group, 2015; Berna et al., 2015; Shah and Huecker, 2019; World Health Organization, 2009):

- High blood pressure, restlessness, sweating, or tremors can be treated with clonidine, an alpha-2 adrenergic agonist (Gowing et al., 2014)
- Digestive symptoms can be treated by anti-emetics (e.g., metoclopramide for nausea or loperamide for diarrhea) or anti-spasmodic (e.g., phloroglucinol)
- Insomnia can be treated by the following non-addictive treatments at bedtime: melatonin agonist, antihistamines, atypical antipsychotics, or sedative tricyclic antidepressants (e.g., amitriptyline and nortriptyline), which can help with pain relief with a reduced risk of dependence associated with benzodiazepines and derivatives (Lie et al., 2015; Nazarian and Park, 2014);
- Muscle pain can be treated by acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or muscle relaxants with no or short-term use of benzodiazepines.

However, from a functional perspective, abrupt or antagonist-induced withdrawal, even under sedation, is not recommended in patients with chronic pain with POUD (Collins et al., 2005; Singh and Basu, 2004). POUD frequently occurs when comorbidities, especially psychiatric or environmental issues, are not considered along with initial pain (Martin et al., 2011) or when opioid prescriptions are renewed without global reassessment. Employing ultra-rapid detoxification poses a risk of increased doctor shopping, illicit drug use, or revealed mental health disorders, especially anxiety disorders, suicidal ideation, and insomnia (Passik et al., 2006). Moreover, some withdrawal symptoms can persist for several months after opioid reduction. In patients experiencing pain, a higher dose and duration of opioid use leads to a concomitantly higher risk of mental health issues, as well as alcohol and other substance use disorders. This further indicates that opioid discontinuation should be progressive and assisted by maintenance treatment in coordination with other prescribers and family

members (Berna et al., 2015; Martin et al., 2011; Soyka et al., 2017). Taking all these factors into consideration suggests that this rapid strategy should only be applied in urgent cases (Dunlap and Cifu, 2016).

### **3.2 Progressive withdrawal**

Gradual opioid analgesic withdrawal is the most common empirical strategy. It is often employed when the opioid use is considered not, or no longer, relevant for chronic pain management (Murphy et al., 2018). This might be related to a lack of efficacy or excessive adverse effects, including drug dependence and OIH. This strategy is relevant when there is drug dependence, misuse, and OIH. Regarding addiction, craving persistence can be a significant obstacle to this strategy. Upon a decision for opioid therapy discontinuation, the opioids should be tapered under medical supervision.

Upon adoption of this strategy, a slow and planned treatment reduction (Rolland et al., 2017) in conjunction with the attending physician is recommended. It is imperative to inform the patient about the clinical withdrawal symptoms that could occur during the treatment decrease, especially those regarding pain. These symptoms could appear during weaning and disappear after a long post-decrease period (Berna et al., 2015). Patients should not be misadvised that there is continuing relevance to continuing opioid analgesic treatment. In case of persistence, the analgesic indication should be reconsidered and the therapeutic options (pharmacological or not) should be reassessed.

There is no validated slow withdrawal protocol. Initially, a transition from immediate-release opioids to a long-acting galenic can be proposed to reduce the brain's peak effect and space out the doses. It has been recognized that pharmacokinetic characteristics, including rapid attainment of peak plasma concentrations, have a significant role in the process of developing dependence (Allain et al., 2015). Subsequently, we propose a progressive gradual withdrawal protocol involving an initial 50% reduction target within the first 3-6 months and complete withdrawal within the next 6-12 months. Other protocols employ different reduction rates ranging from 10% of the total daily dose every day to 10% of the total daily dose every 1-2 weeks (Kahan et al., 2011). However, all protocols promote a decrease rate tailored for the patient's tolerance with stabilization or increased doses, as appropriate.

Upon progressive withdrawal failure, it is important to assess factors that could impede the care, including the potential associated comorbidities. Therefore, it is important to consider the following two strategies, which involve the rotation to a longer half-life opioid that could be more easily stopped (Burma et al., 2017).

### **3.3 Short-term opioid rotation with the progressive withdrawal of the second opioid**

After progressive withdrawal failure, opioids can be rotated to longer half-life alternatives. Suitable alternatives include buprenorphine (combined or not combined with naloxone) and methadone, which are recommended for opioid use disorder management not involving chronic pain (Gowing et al., 2017). Their prolonged binding to mu-opioid receptors prevents the onset of withdrawal symptoms while maintaining the analgesic action. However, there is no established equianalgesic protocol; therefore, it is recommended to conduct progressive titration.

Buprenorphine is a partial mu receptor agonist with pharmacological characteristics requiring a brief initial abrupt withdrawal prior to its introduction with a washout duration of 24-36 hours. Lack of this exposes the patient to a risk of iatrogenic withdrawal syndrome, which is often poorly tolerated and affects the therapeutic relationship (Jones, 2004). Nevertheless, protocols for the introduction of buprenorphine, limiting this washout period without causing withdrawal syndrome, are beginning to be published and practiced more regularly (Ghosh et al., 2019). Buprenorphine has the advantage of reducing the risk of unintentional intoxication by having a limit beyond which it causes no other respiratory effects without losing its analgesic effect (Dahan et al., 2006; Davis, 2012; Khanna and Pillarisetti, 2015). The buprenorphine-naloxone combination reduces the risk of route diversion since naloxone becomes bioavailable only when the tablet is snorted or injected, which blocks the agonist effect of buprenorphine (Harricharan and Farah, 2017).

Methadone allows more flexible handling due to its complete mu receptor agonist profile. Therefore, it could be introduced in parallel with existing opioid analgesics. It is important to slowly titrate it given the high risk of opioid overdose and heart rhythm disorders by QTc prolongation (College of Physicians and Surgeons of British Columbia, 2019; Fredheim et al., 2008; Hawley et al., 2017). Once

a balance of these long half-life treatments has been achieved, the patient can then undergo gradual withdrawal. The chances of a successful withdrawal are improved when it is slower (Dunn et al., 2011; Singh and Basu, 2004). In case of failure, continued long-term long half-life opioid treatment could be considered (Fiellin et al., 2014).

### **3.4 Long-term opioid maintenance treatment**

In case previous strategies fail or if the patient has a comorbid condition that interferes with opioid withdrawal, long-term maintenance opioid therapy could be continued. Similar to the aforementioned notion, the most suitable molecules for this are buprenorphine (+/- naloxone) and methadone. In addition to preventing opioid withdrawal symptoms, increased doses of long-term opioid maintenance treatment effectively reduce craving and the relapse risk (Kakko et al., 2019). Moreover, opioid maintenance treatment blocks the rewarding effects of short-acting opioids through the tolerance mechanism and cross-tolerance, which can, in turn, reduce the craving and loss of control (Kreek, 2006). Properly prescribed methadone and buprenorphine have been shown to enhance retention in treatment, reduce opioid use and overdose mortality, and improve global clinical outcome (Kreek, 2006; Mattick et al., 2014, 2009). Among individuals dependent on prescription opioids, treatment with opioid agonists has been shown to have clear clinical improvement, including substance use, general health, and pain (Weiss et al., 2015). Since addiction is considered a chronic illness with individual and environmental vulnerability factors, pharmacotherapy should be included in comprehensive and continued care through long-term treatment management strategies and continued monitoring (McLellan et al., 2000). Clinical efforts are required to assess the risks and criteria for addiction among patients with chronic pain on opioid medications and to refer to addiction treatment specialists when indicated.

## **4. MANAGING CHRONIC PAIN DURING AND AFTER OPIOID WITHDRAWAL**

As aforementioned, pain exacerbation could occur during the opioid withdrawal period (Wesson and Ling, 2003). This transient exacerbation should be expected as an opioid withdrawal symptom and should not be confused with initial chronic pain. This painful condition is usually spontaneously



resolved without treatment (World Health Organization, 2009). However, in the case of major discomfort, short-term symptomatic analgesic treatment with acetaminophen or NSAIDs could be offered to the patient.

Apart from the withdrawal, management of the initial chronic pain could be problematic. The initial chronic pain, which is responsible for the opioid analgesic prescriptions, could still be present. Different mechanisms, neuropathic, nociplastic, nociceptive, or mixed (associating several mechanisms together) may be at the origin of chronic pain, with symptoms and treatments that may differ according to the type of pain (Christiansen and Cohen, 2018). These elements, with typical examples for each type of pain, are further developed in Table 3. Regardless of the chronic pain type, chronic pain has a complex effect on the patient's biological, psychological, and social spheres that contributes to its persistence; therefore, the drug response alone is rarely sufficient (Fashler et al., 2016; Trouvin and Perrot, 2019; Turk et al., 2011). This is especially the case for patients dependent on opioid analgesics with subsequent limited use of these molecules. Therefore, it is imperative to offer holistic multidisciplinary care to these patients. This multidisciplinary team could include the following professionals: primary care provider, pain physician, addiction and psychiatrist specialists, pharmacist, nurse, psychologist, physical or occupational therapist, and social worker (Center for Substance Abuse Treatment, 2012).

Chronic pain management could vary depending on the adopted opioid withdrawal strategy. Upon the patient being completely weaned off any opioid analgesics, relief should be preferentially sought through the use of non-opioid analgesics and non-pharmacologic therapies. For patients receiving long-term maintenance opioid therapy, adjusting the dosage and administration rate of the opioid agonist treatment might contribute to pain relief if opioid analgesics are recommended (see part 4.2).

The caregiver should use his/her knowledge to educate the patient on the chronic condition and allow them to make informed choices about care. Regardless, the management of these complex conditions depends on the patient- and practitioner-defined objectives at the beginning of the follow-up, which

should avoid the utopian “zero pain” myth that often leads to inflation in the number and dosage of prescribed molecules with subsequent iatrogenic consequences (Lee, 2016).

All the molecules classically used for the analgesic management of chronic pain and mentioned in this article are listed in Table S1 in the Supplemental files.

#### **4.1 Non-opioid analgesics**

This category includes acetaminophen (paracetamol), NSAIDs, and “adjuvant medications.” The latter drugs are initially developed for other therapeutic indications and are found to have analgesic efficacy when administered under certain conditions and are essentially antidepressants and antiepileptic drugs (AEDs). The term “adjuvant” should not be misleading since these medications are now recommended as the first line of therapy depending on the practitioner’s understanding of the mechanism and type of pain (Obata, 2017). It is important to inform the patient about the frequent need to try different “adjuvant medications” so as to determine the one with the best efficacy/tolerance ratio.

##### **4.1.1 Acetaminophen**

Acetaminophen is the most widely used analgesic in the world. Although its mechanism of action remains unclear, it has been reported to involve the endocannabinoid, vanilloid, and calcium channel systems, as well as the cyclooxygenase inhibition and serotonin activation (Mallet et al., 2017). Acetaminophen is recommended as the first-line treatment for many painful conditions given its favorable safety profile compared to other pharmacological alternatives. However, there are limited studies on its efficacy against chronic pain with inconsistent results (Ennis et al., 2016), which encourages its long-term use. There is an ongoing debate on its safety with regard to cardiovascular and gastrointestinal bleeding risks, even at therapeutic doses (McCrae et al., 2018).

##### **4.1.2 NSAIDs**

NSAIDs are heterogeneous, analgesic, antipyretic, and anti-inflammatory medications that are categorized according to their relative selectivity for inhibition of the two types of cyclooxygenase isoenzymes (COX-2 *versus* COX-1) (Herndon and Daniels, 2018). They are known as effective

treatments for nociceptive pain and are commonly used in chronic musculoskeletal pain, especially arthrosis. They are not recognized as effective for neuropathic and nociplastic pain (Derry et al., 2017; Macfarlane et al., 2017; Turk et al., 2011). They are often given as short-term prescriptions seeking the minimum effective doses based on their gastrointestinal and cardiovascular adverse effects (Ho et al., 2018).

#### 4.1.3 Antidepressants

Some antidepressants might have an intrinsic analgesic action regardless of their effectiveness on the initially indicated psychiatric comorbidities (Obata, 2017). The mechanism of action of this analgesic effect remains unclear and is subject to numerous theories seeking to establish its relationship with their thymic action (Nekovarova et al., 2014). The most common hypothesis involves their pain modulation ability through their action on noradrenaline (norepinephrine) and serotonin transporters. This reduces these neurotransmitters' reuptake, which increases their levels in the synaptic cleft. Noradrenaline is believed to have the greatest involvement in the analgesic efficacy of antidepressants, which occurs through the reinforcing effect of the descending inhibitory controls of the pain pathways in the dorsal horn of the spinal cord (Dharmshaktu et al., 2012; Obata, 2017).

Not all antidepressant classes have similar efficacies and pain characteristics. Tricyclic antidepressants have been shown to be effective against resistant headache, neuropathic and nociplastic pain, especially fibromyalgia, with a numbers needed to treat (NNT) i.e., the number of patients who have to be treated to reduce the pain intensity by 50% in 1 patient, of 3.6 (Dharmshaktu et al., 2012; Jackson et al., 2010; Saarto and Wiffen, 2007). This well-studied pharmacological class was until recently recommended as first-line treatment in these contexts. However, its many anticholinergic and histaminergic side effects have caused its gradual replacement with serotonin-norepinephrine reuptake inhibitors (SNRIs) (Baltenberger et al., 2015; Derry et al., 2015a; Moore et al., 2015). Among SNRIs, venlafaxine and duloxetine have been particularly studied in the context of chronic pain. Although their reported NNT varies across studies and the target pathologies, their efficacy has been found to be comparable to that of tricyclic antidepressants and with increased tolerance, which allows them to be

used as first-line treatments for neuropathic and nociplastic chronic pain (Baltenberger et al., 2015; Dharmshaktu et al., 2012; Saarto and Wiffen, 2007). Currently, milnacipran has not been reported to have major efficacy against neuropathic pain; however, it sometimes demonstrates efficacy against nociplastic pain (Cording et al., 2015; Derry et al., 2015b).

Other antidepressants, e.g., serotonin reuptake inhibitors and atypicals, lack significant efficacy against chronic pain. Some studies have reported a higher efficacy compared to placebo; however, these results might be related to their potential efficacy against psychiatric comorbidities associated with chronic pain (see part 5). Therefore, these treatments should be reserved for patients not responding to previously used antidepressants and with thymic symptomatology justifying their use (Baltenberger et al., 2015; Dharmshaktu et al., 2012; Onutu et al., 2018; Patetsos and Horjales-Araujo, 2016; Saarto and Wiffen, 2007).

#### 4.1.4 AEDs

AEDs have demonstrated efficacy against chronic neuropathic pain and some nociplastic pain types, including fibromyalgia (Wiffen et al., 2013b). Upon central or peripheral nervous system injury, these molecules reduce the hyperexcitability of somatosensory pathways responsible for neuropathic pain. Although their mechanism of action remains unclear, it could involve a combination of sodium and calcium channel modulation, glutamate antagonism, and enhancement of the GABA inhibitory system in the peripheral and medullary pain pathways. The mechanism of action of AEDs against fibromyalgia remains poorly understood (Sidhu and Sadhotra, 2016; Turk et al., 2011). Studies have reported inconsistent findings regarding the efficacy of AEDs against chronic neuropathic pain; however, gabapentin, pregabalin, and carbamazepine (Narain and Adcock, 2018; Wiffen et al., 2013b, 2014, 2017) are more commonly used than lacosamide, topiramate, oxcarbazepine, and valproic acid derivatives (Gill et al., 2011; Hearn et al., 2012; Wiffen et al., 2013a; Zhou et al., 2017).

Tolerance to AEDs varies among patients and their side effects are mostly mild (blurred vision, dizziness, asthenia, drowsiness, digestive disorders, euphoria, etc.); however, they frequently lead to premature treatment discontinuation. Reports on serious adverse effects (hematological and

dermatological) remain rare (Wiffen et al., 2013b). Recent guidelines recommend gabapentin-based AEDs as the first-line treatment for chronic neuropathic and nociceptive pain (Cruccu and Truini, 2017; Kia and Choy, 2017; Macfarlane et al., 2017; Mu et al., 2017; Sidhu and Sadhotra, 2016; Wiffen et al., 2013b).

However, recent studies have indicated the potential for abuse and misuse of gabapentinoids, particularly pregabalin, and they should be prescribed with caution in patients with a history of substance use disorder (Ashwini et al., 2015; Driot et al., 2019; Gahr et al., 2013; Saini et al., 2018; Sönmez, 2015; World Health Organization, 2018). Further, a recent Canadian study reported that the concomitant prescription of gabapentin and opioids increased the risk of opioid overdose mortality by 49% (Gomes et al., 2017), which was also found for pregabalin (Gomes et al., 2018).

#### 4.1.5 Other non-opioid analgesics

##### 4.1.5.1 NMDA receptors antagonists

Studies are steadily establishing the involvement of NMDA receptors in the induction and maintenance of chronic pain, particularly neuropathic pain. Initially restricted to a central painful hypersensitization role, recent studies have also demonstrated a peripheral involvement (Petrenko et al., 2003). Studies on NMDA receptor antagonist drugs, including ketamine, methadone, or dextromethorphan, have reported that they could effectively reduce neuropathic pain in some patients not responsive to conventional analgesics (Laumet et al., 2017). Moreover, this analgesic efficacy could be mediated by their reduction action on OIH (see part 2.2.4) (College of Physicians and Surgeons of British Columbia, 2019; Lee et al., 2011).

##### 4.1.5.2 Cannabis and Cannabinoids

Despite being ancestral, the use of cannabis or cannabinoid derivatives remains controversial in chronic pain. There are inconsistent findings regarding their specific analgesic action against pain (Vučković et al., 2018). However, the findings are consistent with regard to the ability of these molecules to improve certain dimensions frequently affected by chronic pain, including sleep, appetite,

anxiety, and the overall quality of life with the latter being considered as the main objective of incurable chronic diseases (Andrade et al., 2019; Romero-Sandoval et al., 2017). In patients with chronic pain and a history of POUD, the use of these potentially addictive drugs requires a proper assessment of the benefit/risk balance and close monitoring (Vučković et al., 2018).

#### 4.1.5.3 Topical agents

Topical agents might provide appropriate pharmacological options as adjuncts or alternatives to oral drugs. Their localized action limits systemic passage and the risk of drug interactions and associated adverse effects (Rudin, 2013; Stanos and Galluzzi, 2013). Their efficacy limits or reduces opioid analgesic use, which is of interest to patients with POUD history. Topical analgesics commonly used for chronic pain treatment are (Derry et al., 2016; Rudin, 2013; Stanos and Galluzzi, 2013):

- Lidocaine, a local anesthetic that blocks fiber A $\delta$  and C to reduce neuropathic pain, which is mainly validated for postherpetic neuralgia with good efficacy and tolerance;
- NSAIDs patches, which are indicated for osteoarthritis disorders with good efficacy and tolerance;
- Capsaicin, an alkaloid responsible for the chili pepper burning sensation whose repeated or high concentration application leads to desensitization of nociceptive fibers in the epidermis with possible reversal of damage nerve fiber degeneration. Capsaicin patches have been mainly found to be effective for neuropathic pain, particularly post-herpetic or HIV-related pain.

#### 4.1.5.4 Skeletal muscle relaxants

Botulinum toxin injections into spastic muscles cause denervation with subsequent myorelaxation. The exact mechanism underlying the resulting pain relief remains unclear. There remains debate on several theories suggesting purely myorelaxation-related relief, modulation of some pain-related peptides, or brain circulation improvement in some pathologies where it is suspected to be the cause of pain (Qerama et al., 2010). The effectiveness of botulinum toxin injections is inconsistent across pain etiologies and seems to fade over time for some patients (Attal et al., 2016; Guzman et al., 2016; Park and Park, 2017; Rivera Día et al., 2014). Therefore, it seems appropriate to remain cautious about this therapeutic option and it cannot be considered as a first-line option in the absence of further studies.

## 4.2 Opioid analgesics

A history of substance use disorders, including for opioids, is not a formal contraindication for opioid analgesic use necessary for acute or chronic pain management (Savage et al., 2008). Although the opioid prescription should be balanced against the associated risks, the equally harmful opiophobia should be avoided (Bennett and Carr, 2002). Opioid analgesic use might be appropriate for managing painful exacerbations regardless of the patient's history. However, it is necessary to consider the prescribing context to limit the patient's risk exposure. It might be preferable to choose a sustained-release galenic to limit the peak effect, which might have some psychoactive side effects, or to choose an abuse-deterrent formulation to control and allow the use of the drug (Allain et al., 2015; Litman et al., 2018; Salwan et al., 2018; Webster and Fine, 2010). The prescriber should seek the minimum effective dose and shortest prescription period with careful monitoring of the treatment's tolerance and effectiveness (see Table 2).

In case withdrawal becomes necessary, POUD management involving long-term substitution with an opioid agonist can be divided into several daily doses to maintain its analgesic effect. In addition to their 24-h substitutive action, these drugs have an additional analgesic effect that might be of interest in a chronic pain context (College of Physicians and Surgeons of British Columbia, 2019; Khanna and Pillarisetti, 2015).

Regarding methadone, its expected analgesic action occurs at 6 hours from the beginning of treatment and after 8 hours when plasma concentrations have stabilized (College of Physicians and Surgeons of British Columbia, 2019; O'Donnell and Vogenberg, 2011; Rajan and Scott-Warren, 2016). The pharmacological characteristics of methadone have several advantages in chronic pain. First, it is a complete opioid agonist, indicating that it can be initiated in conjunction with existing opioid treatment (except for partial agonists such as buprenorphine), including fast-acting drugs for managing painful paroxysms. However, very gradual methadone titration is necessary ("start low, go slow") given its pharmacology, which requires spaced out dose increases to allow stabilization of plasma

concentrations. This precaution significantly improves tolerance and reduces overdose risk (Chou et al., 2014; Hawley et al., 2017; Rajan and Scott-Warren, 2016).

Management of patients with chronic pain treated with buprenorphine (+/- naloxone), a partial opioid receptor agonist, should consider its atypical pharmacological characteristics. Buprenorphine contraindicates any concomitant use of another opioid and is usually used alone to manage both baseline and paroxysmal pain except for very specific emergency situations requiring strong analgesia for major acute pain and under strict supervision by an experienced physician. It is often necessary to split buprenorphine treatment into 3-4 daily doses with an average analgesic efficacy of 6 hours with doses lower than those used in a substitutive indication (Fishman and Kim, 2018; Khanna and Pillarisetti, 2015). Buprenorphine appears to have a better safety profile given its ceiling effect that limits the risk of respiratory depression without losing its analgesic effect, which allows safe dose increases and its use patients at risk of respiratory depression (Dahan et al., 2006; Davis, 2012; Khanna and Pillarisetti, 2015). Moreover, buprenorphine has been reported to be effective in OIH through mechanisms involving kappa-opioid receptor mechanisms (Aiyer et al., 2018; Chen et al., 2014; Khanna and Pillarisetti, 2015).

#### **4.3 Non-pharmacologic therapies**

Taking into account all the biopsychosocial dimensions affected by pain, a holistic approach allows comprehensive addressing of the patient's overall functional alterations and the effects on his/her daily quality of life. The occasionally flawed efficacy and tolerance of pharmacological analgesic therapies might require the use of complementary non-pharmacological approaches. Some of these approaches, which are insufficiently validated, are not financially supported by the health systems. However, they seem to provide a real benefit to patients in terms of perceived quality of life. Their financial cost should be considered, especially for patients most at risk of financial insecurity, including patients with chronic pain with associated comorbidities.

There are numerous so-called "non-drug," "alternative," or "integrative" therapies that come from different specialties. There are guidelines that encourage their use in chronic pain management (Arena



and Jump, 2012; Dowell et al., 2016; Skelly et al., 2018). These recommendations are especially relevant for patients with a substance use disorder history who require alternative strategies to avoid the prescription of addictive drugs. These non-pharmacological approaches can be broadly grouped into several large categories (Bruckenthal, 2010). We only discuss the main ones here.

#### 4.3.1 Neuromodulation

Neuromodulation involves invasive or non-invasive nervous system stimulation (central and/or peripheral) by sending electrical stimuli to alter its activity for pain modulation (Costa et al., 2019; Deer et al., 2019). Spinal cord stimulation is an invasive method that involves electric current application through electrodes implanted in the posterior horn of the spinal cord to modulate pain signals in the brain's pain pathways. The underlying mechanism of action remains unclear. The various parameters (amplitude, pulse width, and frequency) can be adjusted to achieve the desired effect. There are other implantable stimulation techniques that allow nerve conduction modulation at the peripheral level through electrode implantation near the damaged peripheral nerves. Although their effectiveness is inconsistent, these techniques are usually well-tolerated despite some described cases of efficacy loss due to a tolerance phenomenon developing over time (Costa et al., 2019; Deer et al., 2019; Fishman et al., 2019; Nayak and Banik, 2018).

Transcutaneous electrical nerve stimulation is a common analgesic technique that involves the application of a low-intensity electric current using electrodes applied to the skin near the painful area. This electrical stimulation could reduce pain by activating the descending inhibitory pain pathways through partially elucidated mechanisms. Despite its inconsistent efficacy, its good tolerance, low cost, and user-friendliness make it a recommended option for suitable patients (Gibson et al., 2019; Vance et al., 2014).

#### 4.3.2 Evidence-based psychotherapies

Supportive psychotherapy is a commonly used strategy by therapists dealing with patients with chronic pain. It involves empathetic and unreserved validation of the patient's daily life difficulties (Songer, 2005). Its aim is to highlight the patient's difficulties and to strengthen the therapeutic

alliance without attempting in-depth modification of the patient's psychological functioning. Other more specific psychotherapeutic techniques have been shown to be effective in the chronic pain context and might reduce pharmacological therapy use.

Cognitive behavior therapy (CBT) is designed to help patients identify their cognitive distortions and negative behaviors when confronted with a problematic situation. Subsequently, using practical symptom-focused exercises, the therapist assists the patient to improve their emotion regulation and implement adaptation strategies for the initially identified situations. CBT follows relatively standardized protocols that allow its reproducibility and involves assessing the patient's progress during therapy. These characteristics allowed its scientific validation when the method was being expanded for public implementation. The application of this brief therapy in patients with chronic pain disorders could be perfectly integrated into a holistic management approach. CBT works to ameliorate pain-related disability by redirecting the patient's thoughts toward the positive aspects of his or her life. Moreover, it provides support for the management of associated comorbidities (Lim et al., 2018; Urits et al., 2019).

Other psycho-behavioral approaches, including acceptance and commitment therapy (ACT) and mindfulness, are derived from CBT and constitute its third wave (Hayes and Hofmann, 2017). ACT aims to improve the patients' psychological flexibility to allow distancing from and restricting of negative emotions. This allows the patient to free their attention from the pain and avoid its reappearance. Mindfulness exercises are frequently used in ACT to address chronic pain with greater care and detachment. Although it has only been partially validated, these innovative psychotherapeutic approaches represent a valid alternative to CBT for chronic pain management and/or associated comorbidities (Spijkerman et al., 2016; Thorn, 2017; Veehof et al., 2016).

#### 4.3.3 Other complementary approaches

WHO defines these approaches as follows: a broad set of healthcare practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant healthcare system (World Health Organization, 2013). The wide variety of approaches means that they

cannot be exhaustively mentioned; however, they can be grouped into the following four main categories (Bauer et al., 2016; Bruckenthal, 2010; Lee and Raja, 2011):

- Biological-based practices: naturopathy, micro-nutritional, dietary and vitamin supplements, etc.
- Manual therapies: chiropractic, osteopathy, massage, acupuncture, etc.
- Mind-body therapies: sophrology, yoga, tai-chi, hypnosis, etc. Although the overall efficacy of hypnotherapy is still insufficiently validated, recent studies have demonstrated it could be a feasible therapeutic option for patients with chronic pain. Further, this practice is commonly used as a tool in CBT and the subsequent third wave approaches (Elkins et al., 2007; Jensen and Patterson, 2014).

There are obvious overlapping areas between some therapies belonging to several categories. Traditional medicines (e.g., Chinese, Ayurvedic, etc.) can be used as holistic and individualized approaches. However, since they have not been scientifically validated, they cannot be clinically advised. Optimally, these alternative approaches should be conducted by a health professional with validated quality training. Regardless, patients with complex conditions require care management that integrates the validated scientific literature as much as possible, in accordance with the principles of evidence-based medicine and medical ethics. Therefore, caregivers have a role of preventing these vulnerable patients from turning to non-validated care, which is sometimes comparable to sectarian abuses.

#### 4.3.4 Therapeutic education of patients

Therapeutic education of patients aims to help patients with chronic diseases to optimally manage their lives. These workshops are led by health professionals who use the so-called “reverse” pedagogical techniques to obtain patient/caregiver knowledge. Through mobilization of knowledge, resources, and questions regarding their chronic pathology, the patients are allowed to work on their change resistance and play an active role in their care, as well as regain control over their pathology. The application of these techniques to chronic pain has been shown to be effective and facilitates both the

therapeutic alliance and patient compliance with management (Geneen et al., 2015; Vargas-Schaffer and Cogan, 2014).

#### 4.3.5. Physical activity

Patients have long been advised to rest in order to avoid increasing an underlying physical lesion that could increase their pain. However, as knowledge about pain and its consequences have increased, it has become clear that continued physical activity does not increase pain (Geneen et al., 2017), while stopping physical activity is more likely to lead to desocialization, physical deconditioning, and even kinesiophobia, or fear of movement, defined as "an excessive, irrational and debilitating fear to carry out a physical movement, due to a feeling of vulnerability to a painful injury or reinjury" (Knapik et al., 2011). A decrease in the patient's perceived quality of life now makes it advisable to continue physical activity adapted to their abilities and painful feelings rather than to avoid physical activity altogether (Geneen et al., 2017; Luque-Suarez et al., 2019; Puljak and Arienti, 2019).

### 5. HOLISTIC PATIENT MANAGEMENT (Table 4)

Patients with chronic pain frequently present associated comorbid disorders, which are sometimes associated with POUD development (Richard, 2019). These conditions must be identified and treated in candidate patients for opioid prescriptions. Therefore, it is essential to thoroughly interview these patients with complex conditions (see Table 2).

There is a strong association between chronic pain and psychiatric disorders, particularly mood, anxiety, and sleep disorders; however, they remain under-treated in this population (Barry et al., 2016). They have two-way associations, which are underpinned by common morphological and functional alterations (Howe and Sullivan, 2014; Yalcin and Barrot, 2014). It is important to carefully screen for them to avoid unfocused and delayed care. Pain can be prodromal to an emerging depressive syndrome, which leads the therapist to adopt a single analgesic management strategy. This perspective is particularly inappropriate since patients with psychiatric disorders are already at a higher risk of becoming dependent on the opioid prescription (Goesling et al., 2018). From the alternate perspective, the negative effect of chronic pain on the patient's quality of life might lead to

674 secondary psychiatric comorbidity development (Goesling et al., 2018). Central sleep disorders, which  
675 are associated with opioid use rather than psychiatric comorbidity, also have an impact on the overall  
676 perceived quality of life; therefore, they should be assessed through functional exploration (Rose et al.,  
677 2014).

678 Many patients with chronic pain have post-traumatic stress disorder. The high prevalence of this  
679 comorbidity among these patients can be explained by the high frequency of serious accidents or  
680 injuries in the life histories of these patients, which can cause both pain and post-traumatic stress  
681 disorder. Each of these disorders reminds the patient of the other's presence, which reinforces  
682 hypervigilance toward both pain and traumatic events and complicates the patient's management  
683 (Brennstuhl et al., 2015; Morasco et al., 2013; Richard, 2019). Eye movement desensitization and  
684 reprocessing techniques have shown to be effective in the management of this type of comorbid  
685 condition (Valiente-Gómez et al., 2017).

686 Addictive behaviors are frequently associated with both psychiatric disorders and chronic pain.  
687 Chronic pain increases the risk of substance use disorder by two- to five-fold (Howe and Sullivan,  
688 2014). These non-opioid substance use disorder must be carefully screened since they constitute risk  
689 factors for POUD installation and impede the patient's clinical progress (Barry et al., 2016; Richard,  
690 2019).

691 Clinical detection of these comorbidities might be difficult since these syndromes are less  
692 straightforward than the described traditional clinical expressions. Their different symptoms might  
693 potentiate, mix, or fade after interaction with the patient's other pathologies. This might lead to the  
694 management of "co-occurring disorders," which are frequent in psychiatry and addictology, with the  
695 inclusion of the chronic pain pathology (see Figure 1 in Supplemental files) (Edlund et al., 2013;  
696 Flynn and Brown, 2008; Murthy and Chand, 2012; Roncero et al., 2017). The practitioner is faced  
697 with a medley of symptoms that are difficult to discriminate across the different syndromes. Therefore,  
698 it is important to go beyond the conventional care framework involving independent management of  
699 each syndrome. These could involve integrative and simultaneous management where each symptom  
700 dimension is treated by freeing oneself from the referred syndrome(s) (Cuthbert, 2014; Dematteis and

Pennel, 2018; Roncero et al., 2017; Woody, 1996). This holistic approach is limited by the fact that relapse in one dimension might cause a relapse in others. Therefore, there is a need for close and comprehensive patient follow-up involving a multidisciplinary team (Kelly and Daley, 2013). Lacking management of comorbidities associated with chronic pain results in chronicization and exacerbation of pain intensity, which increases the consumption of medical goods (consultations, hospitalizations, additional examinations, travel vouchers, and treatments) and the concomitant cost increase; further, it contributes to a decreased quality of life (Howe and Sullivan, 2014; Roncero et al., 2017).

Holistic management not only focuses on the pathology itself but also on the patient as a whole. The patient can rarely achieve relief by only using drugs, regardless of their dosage. This perspective is particularly relevant in chronic diseases where stabilization, rather than cure, as well as improved overall quality of life, is sought. Therefore, there is a need for a precise assessment of the patient's social situation (Kelly and Daley, 2013; National Institute for Health and Care Excellence Guideline, 2016; Roncero et al., 2017). This is because patients with chronic pain, *a fortiori* those with psychiatric or addictive comorbidities, are frequently faced with a lower than average socio-economic situation and quality of life. These factors can be assessed using scales (Hadi et al., 2019; Marmot et al., 2012; Vartiainen et al., 2016; Webster et al., 2019). The onset of a chronic pain disorder often results in productivity loss and impeded professional activity, which can lead the patient to a precarious livelihood (Dueñas et al., 2016; Patel et al., 2012). A social audit ensures that all the social procedures are properly conducted with anticipation of socio-economic changes to the patients. Social improvement contributes to the patient's psychological well-being and is an objective factor for care progression. The social worker can act as an interface with public service institutions, which might have complex functioning from the patient's perspective (Findley, 2014). This is especially important for ensuring equitable access to care in a clinical setting where opioid analgesic use must be reduced or avoided. Further, this might require the practitioner to use alternative non-pharmacological therapies (see 4.3) whose costs might not be covered by the health system (May et al., 2018; Webster et al., 2019). The intervention of occupational therapists and medicine is an interesting alternative for

allowing adaptation to the patient's workstation and avoid professional disinsertion or allow one to return to work (Désiron et al., 2011; Hesselstrand et al., 2015; Hill, 2016; Lagueux et al., 2018).

Implementation of a holistic care framework requires patient-assisted identification of realistic and possibly quantifiable objectives for care since management onset. These objectives allow for the proposal of a treatment plan that provides a reference guide for the practitioner to avoid "getting lost" in the chronic, complex, multidisciplinary management (Dowell et al., 2016). Moreover, this reference can facilitate the end of the management or discontinuation of some drugs by avoiding an unreasonable therapeutic overstatement and its iatrogenic consequences (World Health Organization, 1994). The general practitioner is at the pivot of this system and allows for care coordination. A fundamental principle is defining "who prescribes what." The most efficient solution is setting up a healthcare service protocol for managing the patient with a pre-determined prescribing doctor and a dispensing pharmacy, which is similar to the management of opioid substitution treatments in addiction (Bertin et al., 2019). This care protocol allows avoiding of nomadic medical behavior and quick detection of overuse. This measure is not intended to be coercive; rather, it prevents complications associated with potential treatment misuse and compliance can be improved through prior therapeutic education of the patient.

From a pharmacological perspective, the co-existence of comorbid pathologies brings a risk of drug inflation, involving different molecules and doses, which should be avoided. This risk is increased if the intervention involves different specialists with different perspectives on the patient. Therefore, effective communication among all the stakeholders and the patient is important to agree on drugs that simultaneously improve several symptom dimensions and limit adverse effects. In patients with a POUD history, there is a need to prevent the risk of dependence and misuse. For example, using an SNRI-type antidepressant could be more relevant than an AED in conjunction with benzodiazepines in a chronic neuropathic pain context associated with the depressive syndrome. Taken together, any treatment started should be regularly evaluated for tolerance and efficacy to avoid the introduction of multiple drugs prescriptions that could be potentially ineffective but with cumulative iatrogenic effects (Aronson, 2006; Dowell et al., 2016; Webster and Fine, 2010; World Health Organization, 1994).

The patient's optimism, which refers to unreserved and unstigmatized pain recognition, as well as the caregivers' empathy, are new factors that could be involved in the positive evolution of the patient's pain symptomatology. These new approaches require further exploration; however, they appear to allow easy implementation and good therapeutic alliance, which are essential for compliance with care (Cánovas et al., 2018; Cohen et al., 2011; Finset and Ørnes, 2017; Koole and Tschacher, 2016).

Holistic management aims to offer the most personalized approach possible to the patient. Therefore, this principle of care evolves over time based on medical advances, social support evolution, and technological progress. The latter provides an interesting possibility for real-life monitoring of the patient's evolution using e- and m-health tools (Luxton et al., 2011; Moss et al., 2019). This real-time approach could potentially allow the patient immediate online access to non-medicinal tools through smartphones, including virtual reality modules, musicotherapy, therapeutic education, meditation, etc. These tools could further relieve the patient's symptoms by avoiding or reducing the associated medication intake.

## **6. CONCLUSION**

Chronic pain management could be complicated by substance use disorder history of one of the used pharmacological classes. Without formalized recommendations, the proposed holistic management (see key points in Table 4) could allow transcending from the conventional care framework, which involves specifically treating each individual pathology, to the global management of all the dimensions affected both by the main pathology and associated comorbidities. This requires that practitioners are able to identify and manage all comorbidities, which generally involves setting up a coordinated, multidisciplinary, and language-shared care network that is tailored for the patient. By taking into account all the dimensions affected by the patient's comorbid conditions, this network aims to improve the overall perceived quality of life by limiting drug inflation.

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1404 **Figure captions (in Supplemental files):**

1405 **Figure 1.** Co-occurring disorders, 4-valent model

**Table 1.** Definitions of the different types of analgesic opioid use disorders

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**Tolerance:**

Physiological adaptation mechanism developed by the organism when confronted with the regular administration of an exogenous substance, leading to habituation to its effects and subsequent progressive loss of efficacy and a need for increased doses to maintain the expected effect.

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**Pharmacodependence:**

State of adaptation of a patient whereby the body has restored its equilibrium to the exogenous substance and is no longer regularly and/or quantitatively supplied, leading to the characteristic appearance of an unpleasant physical and psychological sensation, called withdrawal syndrome.

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**Withdrawal syndrome:**

Unpleasant physical and mental manifestations of inconstant severity and duration, which occur when the substance is in insufficient quantity. In the case of an opioid, classic clinical signs typically include one or more of the following symptoms: lacrimation; rhinorrhea and sneezing; yawning; hot and cold flushes; sweating and piloerection; craving; anxiety; restlessness and irritability; disturbed sleep; gastrointestinal tract symptoms; muscle, bone, and joint aches and pains; headache; muscle cramps; and tremor.

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**Opioid use disorder:**

Dimensional diagnosis which appeared in the 5th edition of the DSM-5, regrouping the categorical notions of dependence, abuse and addiction of the previous edition, characterized by the identification of personal, social, and professional consequences of repeated to compulsive opioid use.

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**Prescribed opioid use disorder:**

Diagnostic nomenclature specific to this work, partially validating the DSM-5 diagnostic criteria of opioid use disorder, of which it could constitute a subtype, where the incriminated substance is prescribed and dispensed for a validated clinical situation, but whose use persists for reasons other than those which led to the initial prescription.

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**Misuse:**

Clinical concept sufficiently broad to encompass most of the aberrant prescribed opioid uses, including individuals who do not meet the criteria for substance use disorder or dependence, referring to all uses other than those for which the drug was prescribed or indicated. "Abuse" occasionally has a similar definition but preferentially refers to non-therapeutic substance use.

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**Addiction:**

A primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors that influence its development and manifestations. Substance addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, 2001).

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**Craving:**

Recent clinical concept, pathognomonic of addiction, characterized by an intense and compulsive desire to use a substance or engage in hedonic behaviors. Persistence of craving is correlated with the risk of relapse of the substance use disorder.

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**Pseudo-addiction:**

Pseudo-addiction refers to the aberrant use of prescribed analgesic treatments by a patient with inadequately managed pain. In this context, pseudo-addiction disappears upon the improvement of analgesic management (Greene and Chambers, 2015; Webster and Fine, 2010)

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DSM-5: *Diagnostic Statistical Manual of Mental Disorders* – 5<sup>th</sup> edition

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**Table 2.** Key points of opioid prescription in chronic pain patients

<i>Start of care - before any opioid prescription</i>
<ul style="list-style-type: none"><li>• Careful screening for associated comorbidities, particularly psychiatric and addictive;</li><li>• If appropriate, use screening or misuse risk assessment scales (POMI and ORT scales);</li><li>• Define precise and ideally quantifiable management objectives;</li><li>• Inform the patient about the expected benefits and potential risks, including drug dependence</li></ul>
<i>Start of care - in case of active opioid prescriptions</i>
<ul style="list-style-type: none"><li>➤ Previous items, to which are added:</li><li>• Find out who is the opioid prescriber;</li><li>• Search for the reason and initial date of opioid prescription;</li><li>• Evaluate the effectiveness and clinical relevance of maintaining treatment;</li><li>• Systematic screening for potential misuse (POMI scale);</li><li>• Screening for opioid analgesic drug dependence.</li></ul>
<i>When opioid is prescribed</i>
<ul style="list-style-type: none"><li>➤ Ensure that the previous items have been completed.</li><li>• Prescribe for the shortest possible time, seeking the minimum dosage;</li><li>• Do not "under-prescribe", at the risk of being ineffective: "Neither too much, nor too little";</li><li>• Promote sustained-release formulations;</li><li>• Anticipate deprescribing by informing the patient about the potential factors for stopping the prescription;</li><li>• Inform the multidisciplinary team of the justified modification of the care;</li><li>• Depending on the situation, protocolization of prescriptions: "Who prescribes what"? ».</li></ul>
<i>After the opioid prescription</i>
<ul style="list-style-type: none"><li>• Check the effectiveness and relevance of the treatment at each consultation;</li><li>• Confront the benefit/risk ratio of opioid treatment with the objectives initially set;</li><li>• Always look for the minimum dosage;</li><li>• Evaluate tolerance and compliance at each visit;</li><li>• Evaluate the occurrence of drug dependence or prescription opioid use disorder at each consultation;</li><li>• If appropriate, repeat the rating of the POMI scale.</li></ul>
POMI: Prescription opioid misuse index; ORT: Opioid risk tool

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**Table 3.** Main characteristics of the different mechanisms of chronic pain

	Type of pain		
	Neuropathic	Nociplastic	Nociceptive
<b>Mechanism(s)</b>	Direct consequence of a lesion or disease affecting the somatosensory system.	Consequence of a supposed alteration in the mechanisms regulating nociception, in the absence of actual or potential damage to the tissue or somatosensory system.	Persistent activation of pain receptors at the ends of nerve fibers, caused by inflammation or mechanical damage to the tissue.
<b>Symptomatology</b>	Various symptoms, frequently: shooting pain, burning sensation, numbness, altered sensitivity and/or sensations that are difficult to describe.	Various and complex clinical presentations; frequently hyperalgesic and allodynic widespread pain.	Function of underlying etiology; often ‘mechanical’ (triggered and aggravated by movement, soothed by rest).
<b>Pharmacologic Treatment(s)</b>	Classical painkillers (acetaminophen and NSAIDs) are of low efficacy; relative efficacy of some antidepressants (tricyclic and serotonin and norepinephrine reuptake inhibitors); gabapentinoid antiepileptics; topical preparations.	Function of the clinical presentation; conventional painkillers are not effective in the long term; avoid opioids (unfavorable risk/benefit balance).	Efficacy of conventional painkillers; long-term use of opioids is questionable (negative risk/benefit balance).
<b>Examples</b>	Peripheral neuropathies: lumbar radiculopathies; postherpetic neuralgia; diabetic neuropathies, HIV-related or post-surgery, etc. Central neuropathies: post-cerebrovascular accident; post-traumatic (spinal cord injury); multiple sclerosis; neurological and metabolic pathologies, etc.	Glossodynia; cluster or tension headaches; irritable bowel syndrome; fibromyalgia; Complex regional pain syndrome, etc.	Rheumatic joint pain (osteoarthritis, arthritis, rheumatoid polyarthritis); chronic low back pain; tendinopathies; bursitis, etc.

NSAIDs: Nonsteroidal anti-inflammatory drugs; HIV: Human immunodeficiency virus



**Table 4.** Key points of holistic care

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- Consideration of all dimensions impacted by the main pathology, but also all associated comorbidities;
  - Multidisciplinary and simultaneous care;
  - Shared-language of the different stakeholders;
  - Personalization of care as close as possible to the patient's needs;
  - Primary objective: overall improvement of the patient's perceived quality of life.
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