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► To cite this version:

Célian Bertin, Noémie Delage, Benjamin Rolland, Lucie Pennel, Mélina Fatseas, et al.. Analgesic opioid use disorders in patients with chronic non-cancer pain: A holistic approach for tailored management. *Neuroscience and Biobehavioral Reviews*, 2021, 121, pp.160 - 174. 10.1016/j.neubiorev.2020.12.015 . hal-03493763

HAL Id: hal-03493763

<https://hal.science/hal-03493763v1>

Submitted on 2 Jan 2023

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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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29 **Declaration of interest:**

30 Célian Bertin, Jessica Delorme, Chouki Chenaf and Nicolas Authier declare that they have no conflict
31 of interest.

32 Noémie Delage received occasional sponsorship to attend scientific meetings from Grünenthal®,
33 Mylan®, Ethypharm® outside the submitted work.

34 Benjamin Rolland received sponsorship to attend scientific meetings and speaker honoraria from
35 Ethypharm®, Indivior®, Camurus®, Recordati®, Grünenthal® outside the submitted work.

36 Lucie Pennel received occasional sponsorship to attend scientific meetings from Lundbeck®,
37 Recordati®, Gilead® outside the submitted work.

38 Mélina Fatseas received occasional sponsorship to attend scientific meetings from Recordati®,
39 Indivior®, Pfizer® outside the submitted work.

40 Anne-Priscille Trouvin reports personal fees to attend scientific meetings and speaker honoraria from
41 Pfizer®, Menarini®, Astellas® and Recordati® outside the submitted work.

42 **Abstract:**

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

55 **Keywords:**

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

57 1. INTRODUCTION

58 The chronic nature of pain makes it a unique pathology regardless of the initial etiology. Acute pain is
59 the response to an essential physiological mechanism which alerts the body when it is at risk of injury.
60 In some patients, this pain may persist, according to various mechanisms (neuropathic, nociplastic or
61 nociceptive), which will be developed later in this manuscript (see part 4). Based on the definition,
62 chronic pain could be defined as experiencing pain for a period exceeding 3-6 months (Institute of
63 Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011). The global
64 prevalence of chronic pain is estimated at 19%-32% (Breivik et al., 2006; Chenaf et al., 2018; Treede
65 et al., 2015). A recent analysis of the National Health Interview Survey conducted by the Center for
66 Disease Control and Prevention estimated that 1 in 5 adults in the USA has chronic pain (Dahlhamer,
67 2018). Chronic pain is among the most common reasons for medical visits and frequently leads to
68 opioid analgesic prescriptions (Dahlhamer, 2018; Daubresse et al., 2013; Treede et al., 2015); further,
69 it has become a major public health issue in two ways. First, it has a high annual economic cost in
70 terms of healthcare and lost productivity, which is estimated at \$560-630 billion per year (Institute of
71 Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011). Second, given
72 the considerable increase in opioid prescription over the past two decades, there has been a
73 concomitant increase in the rates of misuse (21-29%) and addiction (8-12%) in patients with chronic
74 pain (Vowles et al., 2015), which leads to unintentional intoxication and death (Shipton et al., 2018).
75 This trend began in North America before gradually spreading to most of the world's industrialized
76 countries (Agence Nationale de Sécurité du Médicament et des produits de santé, 2019; Chenaf et al.,
77 2016; European Monitoring Centre for Drugs and Drug Addiction, 2018; Gallagher and Galvin, 2018;
78 Häuser et al., 2017; Manchikanti et al., 2018; Van Amsterdam and Van den Brink, 2015) and several
79 developing countries in Africa and Asia (United Nations Office on Drugs and Crime, 2018).
80 Depending on the criteria used, a literature review conducted by Højsted and Sjøgren (2007) reported
81 that the prevalence of prescription opioid problematic behavior in patients with chronic non-cancer
82 pain was up to 50%. Further, this risk is increased among patients with associated comorbidities,

83 particularly psychiatric and addictive, which are common in patients with chronic pain (Barry et al.,
84 2016; Barth et al., 2013).

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

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

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

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

103 The diagnosis of opioid use disorder appeared in the 5th version of the *Diagnostic Statistical Manual*
104 *of Mental Disorders* (DSM), (American Psychiatric Association, 2013; Hasin et al., 2013), and
105 combines the categorical diagnoses of abuse, dependence and addiction from the previous edition,
106 which continue to be used frequently (Substance Abuse and Mental Health Services Administration,
107 2016). This evolution corresponds to the clinically observed continuum, which focuses not on the

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

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

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

131 **2.1 Tolerance, pharmacodependence and withdrawal syndrome**

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

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

147 **2.2 Problematic use of prescription analgesic opioids**

148 2.2.1 Misuse and abuse

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

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

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

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

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

178 2.2.2 Addiction

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

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

188 The concept of craving is a central element in this definition and in addiction assessment. It is
189 characterized by an intense and compulsive desire to use a substance or engage in hedonic behaviors.
190 Craving has been recently identified as a central concept and clinically relevant feature in addictive
191 behavior and is included in the DSM-5 criteria. Laboratory (Carter and Tiffany, 1999; Childress et al.,
192 2008) and daily life studies using ecological momentary assessment approaches have demonstrated a
193 relationship among craving episodes, substance use, and relapse risk (Fatseas et al., 2015; Serre et al.,
194 2015). There is a clear difference between a craving and physical dependence with the latter being
195 related to physiological adaptation to chronic opioid exposure. Conversely, whereas physical signs of
196 withdrawal, or physical tolerance to opioids that the body may have gradually developed, disappear
197 quickly and naturally after opioid abstinence, craving can persist years after opioid discontinuation.
198 This persistence of craving is a relapse risk factor that increases the risk of overdose in a patient who is
199 physically withdrawn from opioids and, thus, has a tolerance that has dissipated. The management,
200 particularly pharmacological, of opioid withdrawal promotes a better control of craving and reduces
201 the risk of relapse and overdose (Kakko et al., 2019; Kreek, 2006).

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

205 2.2.3 Pseudo-addiction

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

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

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

215 2.2.4 Opioid-induced hyperalgesia

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

220 This paradoxical body reaction could be confused with the tolerance phenomenon since they both
221 involve reduced opioid analgesic response (Hayhurst and Durieux, 2016). However, unlike in
222 tolerance phenomenon, patients with OIH report no or very short-term pain relief upon increased
223 doses. Finally, it is generally associated with a higher pain intensity than that initially reported with
224 generalized, diffuse, and poorly systematized complaints (Lee et al., 2011; Ramasubbu and Gupta,
225 2011). OIH generally occurs faster than the tolerance phenomenon; further, its pathophysiological
226 mechanism remains unclear (Raffa and Pergolizzi, 2013). There is no consensus on OIH management;
227 however, it mostly involves progressive withdrawal strategies, opioid rotation, use of N-methyl-D-
228 aspartate (NMDA) antagonists, e.g., ketamine, methadone, or dextromethorphan, as well as other non-
229 opioid pharmacological and non-pharmacological strategies (Lee et al., 2011; Ramasubbu and Gupta,
230 2011; Yi and Pryzbylkowski, 2015).

231 **3. DIFFERENT STRATEGIES FOR MANAGING PRESCRIBED OPIOID USE DISORDERS**

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

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

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

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

263 **3.1 Abrupt withdrawal**

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

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

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

289 members (Berna et al., 2015; Martin et al., 2011; Soyka et al., 2017). Taking all these factors into
290 consideration suggests that this rapid strategy should only be applied in urgent cases (Dunlap and Cifu,
291 2016).

292 **3.2 Progressive withdrawal**

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

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

306 There is no validated slow withdrawal protocol. Initially, a transition from immediate-release opioids
307 to a long-acting galenic can be proposed to reduce the brain's peak effect and space out the doses. It
308 has been recognized that pharmacokinetic characteristics, including rapid attainment of peak plasma
309 concentrations, have a significant role in the process of developing dependence (Allain et al., 2015).
310 Subsequently, we propose a progressive gradual withdrawal protocol involving an initial 50%
311 reduction target within the first 3-6 months and complete withdrawal within the next 6-12 months.
312 Other protocols employ different reduction rates ranging from 10% of the total daily dose every day to
313 10% of the total daily dose every 1-2 weeks (Kahan et al., 2011). However, all protocols promote a
314 decrease rate tailored for the patient's tolerance with stabilization or increased doses, as appropriate.

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

319 **3.3 Short-term opioid rotation with the progressive withdrawal of the second opioid**

320 After progressive withdrawal failure, opioids can be rotated to longer half-life alternatives. Suitable
321 alternatives include buprenorphine (combined or not combined with naloxone) and methadone, which
322 are recommended for opioid use disorder management not involving chronic pain (Gowing et al.,
323 2017). Their prolonged binding to mu-opioid receptors prevents the onset of withdrawal symptoms
324 while maintaining the analgesic action. However, there is no established equianalgesic protocol;
325 therefore, it is recommended to conduct progressive titration.

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

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

341 a balance of these long half-life treatments has been achieved, the patient can then undergo gradual
342 withdrawal. The chances of a successful withdrawal are improved when it is slower (Dunn et al.,
343 2011; Singh and Basu, 2004). In case of failure, continued long-term long half-life opioid treatment
344 could be considered (Fiellin et al., 2014).

345 **3.4 Long-term opioid maintenance treatment**

346 In case previous strategies fail or if the patient has a comorbid condition that interferes with opioid
347 withdrawal, long-term maintenance opioid therapy could be continued. Similar to the aforementioned
348 notion, the most suitable molecules for this are buprenorphine (+/- naloxone) and methadone. In
349 addition to preventing opioid withdrawal symptoms, increased doses of long-term opioid maintenance
350 treatment effectively reduce craving and the relapse risk (Kakko et al., 2019). Moreover, opioid
351 maintenance treatment blocks the rewarding effects of short-acting opioids through the tolerance
352 mechanism and cross-tolerance, which can, in turn, reduce the craving and loss of control (Kreek,
353 2006). Properly prescribed methadone and buprenorphine have been shown to enhance retention in
354 treatment, reduce opioid use and overdose mortality, and improve global clinical outcome (Kreek,
355 2006; Mattick et al., 2014, 2009). Among individuals dependent on prescription opioids, treatment
356 with opioid agonists has been shown to have clear clinical improvement, including substance use,
357 general health, and pain (Weiss et al., 2015). Since addiction is considered a chronic illness with
358 individual and environmental vulnerability factors, pharmacotherapy should be included in
359 comprehensive and continued care through long-term treatment management strategies and continued
360 monitoring (McLellan et al., 2000). Clinical efforts are required to assess the risks and criteria for
361 addiction among patients with chronic pain on opioid medications and to refer to addiction treatment
362 specialists when indicated.

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

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

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

370 Apart from the withdrawal, management of the initial chronic pain could be problematic. The initial
371 chronic pain, which is responsible for the opioid analgesic prescriptions, could still be present.
372 Different mechanisms, neuropathic, nociplastic, nociceptive, or mixed (associating several
373 mechanisms together) may be at the origin of chronic pain, with symptoms and treatments that may
374 differ according to the type of pain (Christiansen and Cohen, 2018). These elements, with typical
375 examples for each type of pain, are further developed in Table 3. Regardless of the chronic pain type,
376 chronic pain has a complex effect on the patient's biological, psychological, and social spheres that
377 contributes to its persistence; therefore, the drug response alone is rarely sufficient (Fashler et al.,
378 2016; Trouvin and Perrot, 2019; Turk et al., 2011). This is especially the case for patients dependent
379 on opioid analgesics with subsequent limited use of these molecules. Therefore, it is imperative to
380 offer holistic multidisciplinary care to these patients. This multidisciplinary team could include the
381 following professionals: primary care provider, pain physician, addiction and psychiatrist specialists,
382 pharmacist, nurse, psychologist, physical or occupational therapist, and social worker (Center for
383 Substance Abuse Treatment, 2012).

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

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

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

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

396 **4.1 Non-opioid analgesics**

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

404 4.1.1 Acetaminophen

405 Acetaminophen is the most widely used analgesic in the world. Although its mechanism of action
406 remains unclear, it has been reported to involve the endocannabinoid, vanilloid, and calcium channel
407 systems, as well as the cyclooxygenase inhibition and serotonin activation (Mallet et al., 2017).

408 Acetaminophen is recommended as the first-line treatment for many painful conditions given its
409 favorable safety profile compared to other pharmacological alternatives. However, there are limited
410 studies on its efficacy against chronic pain with inconsistent results (Ennis et al., 2016), which
411 encourages its long-term use. There is an ongoing debate on its safety with regard to cardiovascular
412 and gastrointestinal bleeding risks, even at therapeutic doses (McCrae et al., 2018).

413 4.1.2 NSAIDs

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

417 treatments for nociceptive pain and are commonly used in chronic musculoskeletal pain, especially
418 arthrosis. They are not recognized as effective for neuropathic and nociplastic pain (Derry et al., 2017;
419 Macfarlane et al., 2017; Turk et al., 2011). They are often given as short-term prescriptions seeking the
420 minimum effective doses based on their gastrointestinal and cardiovascular adverse effects (Ho et al.,
421 2018).

422 4.1.3 Antidepressants

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

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

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

447 Other antidepressants, e.g., serotonin reuptake inhibitors and atypicals, lack significant efficacy
448 against chronic pain. Some studies have reported a higher efficacy compared to placebo; however,
449 these results might be related to their potential efficacy against psychiatric comorbidities associated
450 with chronic pain (see part 5). Therefore, these treatments should be reserved for patients not
451 responding to previously used antidepressants and with thymic symptomatology justifying their use
452 (Baltenberger et al., 2015; Dharmshaktu et al., 2012; Onutu et al., 2018; Patetsos and Horjales-Araujo,
453 2016; Saarto and Wiffen, 2007).

454 4.1.4 AEDs

455 AEDs have demonstrated efficacy against chronic neuropathic pain and some nociplastic pain types,
456 including fibromyalgia (Wiffen et al., 2013b). Upon central or peripheral nervous system injury, these
457 molecules reduce the hyperexcitability of somatosensory pathways responsible for neuropathic pain.
458 Although their mechanism of action remains unclear, it could involve a combination of sodium and
459 calcium channel modulation, glutamate antagonism, and enhancement of the GABA inhibitory system
460 in the peripheral and medullary pain pathways. The mechanism of action of AEDs against
461 fibromyalgia remains poorly understood (Sidhu and Sadhotra, 2016; Turk et al., 2011). Studies have
462 reported inconsistent findings regarding the efficacy of AEDs against chronic neuropathic pain;
463 however, gabapentin, pregabalin, and carbamazepine (Narain and Adcock, 2018; Wiffen et al., 2013b,
464 2014, 2017) are more commonly used than lacosamide, topiramate, oxcarbazepine, and valproic acid
465 derivatives (Gill et al., 2011; Hearn et al., 2012; Wiffen et al., 2013a; Zhou et al., 2017).

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

469 dermatological) remain rare (Wiffen et al., 2013b). Recent guidelines recommend gabapentin-based
470 AEDs as the first-line treatment for chronic neuropathic and nociplastic pain (Cruccu and Truini,
471 2017; Kia and Choy, 2017; Macfarlane et al., 2017; Mu et al., 2017; Sidhu and Sadhotra, 2016; Wiffen
472 et al., 2013b).

473 However, recent studies have indicated the potential for abuse and misuse of gabapentinoids,
474 particularly pregabalin, and they should be prescribed with caution in patients with a history of
475 substance use disorder (Ashwini et al., 2015; Driot et al., 2019; Gahr et al., 2013; Saini et al., 2018;
476 Sönmez, 2015; World Health Organization, 2018). Further, a recent Canadian study reported that the
477 concomitant prescription of gabapentin and opioids increased the risk of opioid overdose mortality by
478 49% (Gomes et al., 2017), which was also found for pregabalin (Gomes et al., 2018).

479 4.1.5 Other non-opioid analgesics

480 4.1.5.1 NMDA receptors antagonists

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

489 4.1.5.2 Cannabis and Cannabinoids

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

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

498 4.1.5.3 Topical agents

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

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

511 4.1.5.4 Skeletal muscle relaxants

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

520 **4.2 Opioid analgesics**

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

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

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

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

547 Management of patients with chronic pain treated with buprenorphine (+/- naloxone), a partial opioid
548 receptor agonist, should consider its atypical pharmacological characteristics. Buprenorphine
549 contraindicates any concomitant use of another opioid and is usually used alone to manage both
550 baseline and paroxysmal pain except for very specific emergency situations requiring strong analgesia
551 for major acute pain and under strict supervision by an experienced physician. It is often necessary to
552 split buprenorphine treatment into 3-4 daily doses with an average analgesic efficacy of 6 hours with
553 doses lower than those used in a substitutive indication (Fishman and Kim, 2018; Khanna and
554 Pillarisetti, 2015). Buprenorphine appears to have a better safety profile given its ceiling effect that
555 limits the risk of respiratory depression without losing its analgesic effect, which allows safe dose
556 increases and its use patients at risk of respiratory depression (Dahan et al., 2006; Davis, 2012;
557 Khanna and Pillarisetti, 2015). Moreover, buprenorphine has been reported to be effective in OIH
558 through mechanisms involving kappa-opioid receptor mechanisms (Aiyer et al., 2018; Chen et al.,
559 2014; Khanna and Pillarisetti, 2015).

560 **4.3 Non-pharmacologic therapies**

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

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

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

575 4.3.1 Neuromodulation

576 Neuromodulation involves invasive or non-invasive nervous system stimulation (central and/or
577 peripheral) by sending electrical stimuli to alter its activity for pain modulation (Costa et al., 2019;
578 Deer et al., 2019). Spinal cord stimulation is an invasive method that involves electric current
579 application through electrodes implanted in the posterior horn of the spinal cord to modulate pain
580 signals in the brain's pain pathways. The underlying mechanism of action remains unclear. The
581 various parameters (amplitude, pulse width, and frequency) can be adjusted to achieve the desired
582 effect. There are other implantable stimulation techniques that allow nerve conduction modulation at
583 the peripheral level through electrode implantation near the damaged peripheral nerves. Although their
584 effectiveness is inconsistent, these techniques are usually well-tolerated despite some described cases
585 of efficacy loss due to a tolerance phenomenon developing over time (Costa et al., 2019; Deer et al.,
586 2019; Fishman et al., 2019; Nayak and Banik, 2018).

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

593 4.3.2 Evidence-based psychotherapies

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

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

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

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

619 4.3.3 Other complementary approaches

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

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

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

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

641 4.3.4 Therapeutic education of patients

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

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

650 4.3.5. Physical activity

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

660 **5. HOLISTIC PATIENT MANAGEMENT (Table 4)**

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

665 There is a strong association between chronic pain and psychiatric disorders, particularly mood,
666 anxiety, and sleep disorders; however, they remain under-treated in this population (Barry et al.,
667 2016). They have two-way associations, which are underpinned by common morphological and
668 functional alterations (Howe and Sullivan, 2014; Yalcin and Barrot, 2014). It is important to carefully
669 screen for them to avoid unfocused and delayed care. Pain can be prodromal to an emerging
670 depressive syndrome, which leads the therapist to adopt a single analgesic management strategy. This
671 perspective is particularly inappropriate since patients with psychiatric disorders are already at a
672 higher risk of becoming dependent on the opioid prescription (Goesling et al., 2018). From the
673 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

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

708 Holistic management not only focuses on the pathology itself but also on the patient as a whole. The
709 patient can rarely achieve relief by only using drugs, regardless of their dosage. This perspective is
710 particularly relevant in chronic diseases where stabilization, rather than cure, as well as improved
711 overall quality of life, is sought. Therefore, there is a need for a precise assessment of the patient's
712 social situation (Kelly and Daley, 2013; National Institute for Health and Care Excellence Guideline,
713 2016; Roncero et al., 2017). This is because patients with chronic pain, *a fortiori* those with
714 psychiatric or addictive comorbidities, are frequently faced with a lower than average socio-economic
715 situation and quality of life. These factors can be assessed using scales (Hadi et al., 2019; Marmot et
716 al., 2012; Vartiainen et al., 2016; Webster et al., 2019). The onset of a chronic pain disorder often
717 results in productivity loss and impeded professional activity, which can lead the patient to a
718 precarious livelihood (Dueñas et al., 2016; Patel et al., 2012). A social audit ensures that all the social
719 procedures are properly conducted with anticipation of socio-economic changes to the patients. Social
720 improvement contributes to the patient's psychological well-being and is an objective factor for care
721 progression. The social worker can act as an interface with public service institutions, which might
722 have complex functioning from the patient's perspective (Findley, 2014). This is especially important
723 for ensuring equitable access to care in a clinical setting where opioid analgesic use must be reduced
724 or avoided. Further, this might require the practitioner to use alternative non-pharmacological
725 therapies (see 4.3) whose costs might not be covered by the health system (May et al., 2018; Webster
726 et al., 2019). The intervention of occupational therapists and medicine is an interesting alternative for

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

729 Implementation of a holistic care framework requires patient-assisted identification of realistic and
730 possibly quantifiable objectives for care since management onset. These objectives allow for the
731 proposal of a treatment plan that provides a reference guide for the practitioner to avoid "getting lost"
732 in the chronic, complex, multidisciplinary management (Dowell et al., 2016). Moreover, this reference
733 can facilitate the end of the management or discontinuation of some drugs by avoiding an
734 unreasonable therapeutic overstatement and its iatrogenic consequences (World Health Organization,
735 1994). The general practitioner is at the pivot of this system and allows for care coordination. A
736 fundamental principle is defining "who prescribes what." The most efficient solution is setting up a
737 healthcare service protocol for managing the patient with a pre-determined prescribing doctor and a
738 dispensing pharmacy, which is similar to the management of opioid substitution treatments in
739 addiction (Bertin et al., 2019). This care protocol allows avoiding of nomadic medical behavior and
740 quick detection of overuse. This measure is not intended to be coercive; rather, it prevents
741 complications associated with potential treatment misuse and compliance can be improved through
742 prior therapeutic education of the patient.

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

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

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

767 **6. CONCLUSION**

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

777 **Funding:**

778 This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-
779 profit sectors.

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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

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.

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.

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.

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.

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.

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.

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).

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.

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)

DSM-5: *Diagnostic Statistical Manual of Mental Disorders – 5th edition*

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

Start of care - before any opioid prescription

- Careful screening for associated comorbidities, particularly psychiatric and addictive;
- If appropriate, use screening or misuse risk assessment scales (POMI and ORT scales);
- Define precise and ideally quantifiable management objectives;
- Inform the patient about the expected benefits and potential risks, including drug dependence

Start of care - in case of active opioid prescriptions

➤ Previous items, to which are added:

- Find out who is the opioid prescriber;
- Search for the reason and initial date of opioid prescription;
- Evaluate the effectiveness and clinical relevance of maintaining treatment;
- Systematic screening for potential misuse (POMI scale);
- Screening for opioid analgesic drug dependence.

When opioid is prescribed

➤ Ensure that the previous items have been completed.

- Prescribe for the shortest possible time, seeking the minimum dosage;
- Do not "under-prescribe", at the risk of being ineffective: "Neither too much, nor too little";
- Promote sustained-release formulations;
- Anticipate deprescribing by informing the patient about the potential factors for stopping the prescription;
- Inform the multidisciplinary team of the justified modification of the care;
- Depending on the situation, protocolization of prescriptions: "Who prescribes what"? ».

After the opioid prescription

- Check the effectiveness and relevance of the treatment at each consultation;
- Confront the benefit/risk ratio of opioid treatment with the objectives initially set;
- Always look for the minimum dosage;
- Evaluate tolerance and compliance at each visit;
- Evaluate the occurrence of drug dependence or prescription opioid use disorder at each consultation;
- If appropriate, repeat the rating of the POMI scale.

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
Mechanism(s)	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.
Symptomatology	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).
Pharmacologic Treatment(s)	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).
Examples	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

- 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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