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RESEARCH ARTICLE

Chronic opioid therapy in long-term cancer survivors

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Abstract
Purpose Long-term cancer survivors develop special health issues and specific needs. Chronic pain, whether the consequence of their cancer or as a side effect of treatment, is one of their most prevalent concerns.
Methods We conducted a review of the English-language literature on long-term cancer survivorship and chronic opioid therapy, with the objective of determining the efficacy, safety and tolerability in this group of patients. Practical management recommendations are made on the basis of this review.
Results Pain syndromes encountered in the long-term cancer survivors are diverse. Opioid receptor pathways possess complex and pleiotropic functions and continuous over-activation may lead to de novo endocrinopathies, immunosuppression, neurocognitive impairment, or cell cycle disturbances with potential clinical connotations. However, there are insufficient data to support evidence-based decision making with respect to patient selection, doses, administration, monitoring and follow-up. Data about long-term treatment effectiveness and safety are limited and often aggravated by the overlapping of several diseases prevalent among long-term cancer survivors, as well as chronic opiate-induced toxicity.
Conclusions Chronic opioid therapy is frequent in long-term cancer survivors, and may negatively affect the immune system, and produce health problems such as endocrinopathies, osteoporosis, neurological or cardiopulmonary effects, alterations of cell cycle kinetics, abuse and addiction. This review highlights the need for specialized teams to treat chronic pain in long-term cancer survivors from an integrative perspective.

Keywords Cancer · Survivors · Opioids · Chronic pain · Chronic opioid therapy

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Introduction

According to the EUROCARE-5 population-based study, 5-year overall survival has risen steadily for all European regions and exceeds 60 % for the most common tumors [1]. As a result, over 100,000 new long-term cancer survivors will be recorded every year in a medium-sized, Western country like Spain [2]. In North America, the number of long-term cancer survivors has also increased in

the last three decades, such that in 2012 there were more than 13 million [3–5]. Projections are that in the next 40 years, there will be twice as many long-term cancer survivors over 65 years of age. The problems affecting these patients already represent a growing, global public health challenge.

The American Cancer Society (ACS) defines "long-term cancer survivor" as any patient who has survived 5 years or more following a diagnosis of cancer [6]. These individuals exhibit different, specific health concerns and needs involving physical, social, occupational, psychological, and emotional domains. Thus, they are more prone to develop metabolic syndrome, endocrinopathies, cardiovascular diseases, osteoporosis, psychological disorders, and neurocognitive impairment. Among the most relevant health needs, we highlight the control of symptoms and sequelae associated with cancer and treatment, surveillance for disease relapse or second tumors, as well as the prevention and management of the aforementioned diseases.

Chronic pain is present in 5 to 56 % of all long-term cancer survivors. In fact, it is one of the most prevalent symptoms [7, 8], while other common complaints include mood disorders and fatigue [9–13]. This wide range of prevalence rates can depend on cancer subtype, treatments received, pain metric, and time since completion of oncological therapy. The prevalence and severity of pain are expected to decrease over time, but despite tissue integrity, complete recovery is sometimes never achieved. For example, in one study of women with breast cancer that assessed the presence of pain at 40 months and 10 years from the end of antineoplastic treatment, 27 and 32 % ($p < 0.05$) reported above-average chronic pain, respectively; whereas only 25 % labeled it as improved [10]. Exercise interventions and weight control are proposed to palliate long-term pain in these women. However, pain rates tend to be higher than in the general population [11, 14]. In such cases, chronic pain remains as a reminder of the past, hindering adaptation. It will have profound repercussions on social and family relations, return to work, and quality of life.

Pain syndromes encountered in the long-term cancer survivors are diverse in etiology and nature. The most frequent causes include surgical complications (e.g., post-operative pain syndromes such as post-mastectomy or post-thoracotomy pain, phantom limb, etc.), radiotherapy (such as plexopathies, insufficiency fractures, or osteoradionecrosis), chemotherapy (like painful peripheral neuropathy), or hormone therapy (for instance, aromatase inhibitor-induced arthralgia). Table 1 more fully enumerates pain etiologies in cancer survivors. In some individuals suffering from chronic pain, therapeutic alternatives such as adjuvant treatments (e.g., antidepressants or anticonvulsants), invasive pain management techniques (for example, sympathetic blocks, epidural catheters, plexus, peripheral nerve, or epidural infiltrations, etc.), or psychological approaches will be unsuccessful; hence, chronic opioid administration will be necessary.

With this review, we seek to analyze the available evidence of chronic opioid treatment effectiveness and safety in long-term cancer survivors, within the context of their particularities, concerns, and special healthcare needs, so as to generate practical management recommendations.

Methods

We conducted a review of the English-language literature on long-term cancer survivorship and chronic opioid therapy, with the objective of determining the efficacy, safety and tolerability of prolonged opioid use in this group of patients. As a secondary aim, we have reviewed the effects on specific systems or organs in long-term cancer survivors. The search was carried out using the following electronic databases: PubMed, EMBASE, The Cochrane Library, and Google Scholar. The period of interest was 1980–2015. A primary data review process comprised combinations, using Boolean operators (i.e. "AND", "OR") of the following medical subject heading (MeSH) terms and key words: survivor, cancer, tumor, pain, chronic, analgesics, opioid, opiate alkaloids, morphine, methadone, fentanyl, hydromorphone, oxycodone, oxymorphone, tramadol, and tapentadol. Truncated and wildcard search was applied as needed. Additional references were obtained from a secondary search, including other MESH terms related to common health issues in patients receiving chronic opioids: addictive behavior, drug dependence, substance use disorders, drug abuse, long-term adverse effects, survivors, medication therapy management, opioid analgesics, opioid replacement therapy, endocrine disease, hypogonadism, androgen, testosterone, glucocorticoids, hydrocortisone, return to work, employment, opioid receptor, cell proliferation, apoptosis, immunosuppression, cardiovascular diseases, neurocognitive disorder, osteoporosis, neurotoxicity syndrome, recurrence and mortality. The results of both searches were combined and duplicates were removed. Each reference was critically reviewed by two of the authors (ARV and RSB) applying the selection criteria that (a) the manuscripts provided clinical or biological information of use for the physicians having to make decisions or (b) that they contributed to enhance the existing conceptual and theoretical framework regarding this particular patient population. References on preclinical or in vitro data were accepted if they were thought to trigger the development of new treatment strategies for these patients. We excluded articles focused on pediatric population, studies with no

Table 1 Pain etiology in long-term cancer survivors

Affected system	Pain syndrome	Comments
Neurological	Chemotherapy-induced peripheral neuropathy	A common side effect of several cytotoxics, such as platinum compounds, taxanes, and vinca alkaloids [167]
	Post-operative pain syndrome	Post-thoracotomy, post-mastectomy [168]
	Lumbosacral or brachial plexopathy, secondary to radiotherapy, brachytherapy or surgery	Brachial plexopathy is more prevalent. It can develop decades after treatment [169]
	Post-herpetic neuralgia	Cancer patients are at considerably increased risk of herpes zoster; complications are common [170]
Rheumatological	Myalgia and non-inflammatory migrating arthralgia	Secondary to tamoxifen, aromatase inhibitors, corticosteroid withdrawal [171]
Lymphatic	Lymphedema-related disturbances	Common in patients with breast cancer, is associated pain, emotional distress, and worse quality of life [172]
Skeletal	Osteoporosis	Several treatments (chemotherapy, hormone therapy, corticosteroids, opioids) cause osteoporosis directly or indirectly (hypogonadism, early menopause) [21, 141]
	Osteonecrosis (femoral and humeral head, knee)	Increased risk several years after hematopoietic stem cell transplantation [173] Corticosteroids are often prescribed for cancer patients [174]
	Bisphosphonate-associated osteonecrosis of the jaw	Mainly in patients with >36 months exposure to pamidronate or zoledronic acid, >65 years, and previous dental problems [175]
	Pelvic insufficiency fracture	Associated with pelvic radiotherapy for gynecological or rectal cancers; patients present with pelvic pain [176]
Muscular	Rotator cuff tendinitis	>70 % of patients complain of pain after radical neck dissection [177]
	Surgical cervical lymphadenectomy	
	Adhesive capsulitis ("frozen shoulder")	Characterized by spontaneous shoulder pain, progressive stiffness, and disability, it is relatively frequent after axillary lymph node dissection [178]
Gastrointestinal	Enteritis, proctitis	Typically associated with diarrhea and fecal urgency resulting from radiotherapy [179]
Genitourinary	Chronic pelvic pain	Symptom of colorectal, genitourinary cancer, tumors involving pelvic lymph nodes or pelvic bones
	Cystitis	Generally associated with frequency, urgency, and urge incontinence due to radiotherapy or chemotherapy
	Dyspareunia	Secondary to menopause or vaginal dryness because of radiotherapy [180]

assessment of opiate therapy or not applicable to cancer survivors, and references published before 1980. In addition, we excluded case reports, comments, editorials and communications to congress.

26,873 records were screened, 26,773 of which were excluded following the aforementioned criteria. Figure 1 shows a flow diagram of the article selection process. Finally, our appraisal of the literature found 100 studies that were retrieved for full-text evaluation. Most were clinical cohort studies ($n = 38$) [15–52], case–control studies ($n = 8$) [53–60], population-based cohorts ($n = 3$) [61–63] but there were also 35 in vitro studies [64–98], investigations in animal models ($n = 11$) [99–109], and there were only 5 clinical trials [110–114]. The main purpose of each article is summarized in Table 2. The text states when the data to support this revision come from non-cancer pain syndromes. The criterion to include these articles ($n = 35$) is that their potential relevance (social or occupation aspects, addiction, mortality, etc.) exceed the uncertainty as to being able to extrapolate to other groups.

To make this material easier to grasp, the information was analyzed and categorized into: efficacy and safety, effects of opioids on the immune system, endocrine system, cell kinetics, bone health, nervous system, cardiopulmonary effects, social and occupational aspects, overall mortality, and abuse and addiction. Finally, practical management recommendations are made on the basis of this review and have been agreed upon by all the authors of this document.

Efficacy and safety of long-term opioid therapy

Long-term efficacy data

The review found that opioids can be very effective for short-term treatment of acute, severe pain, but the effects of

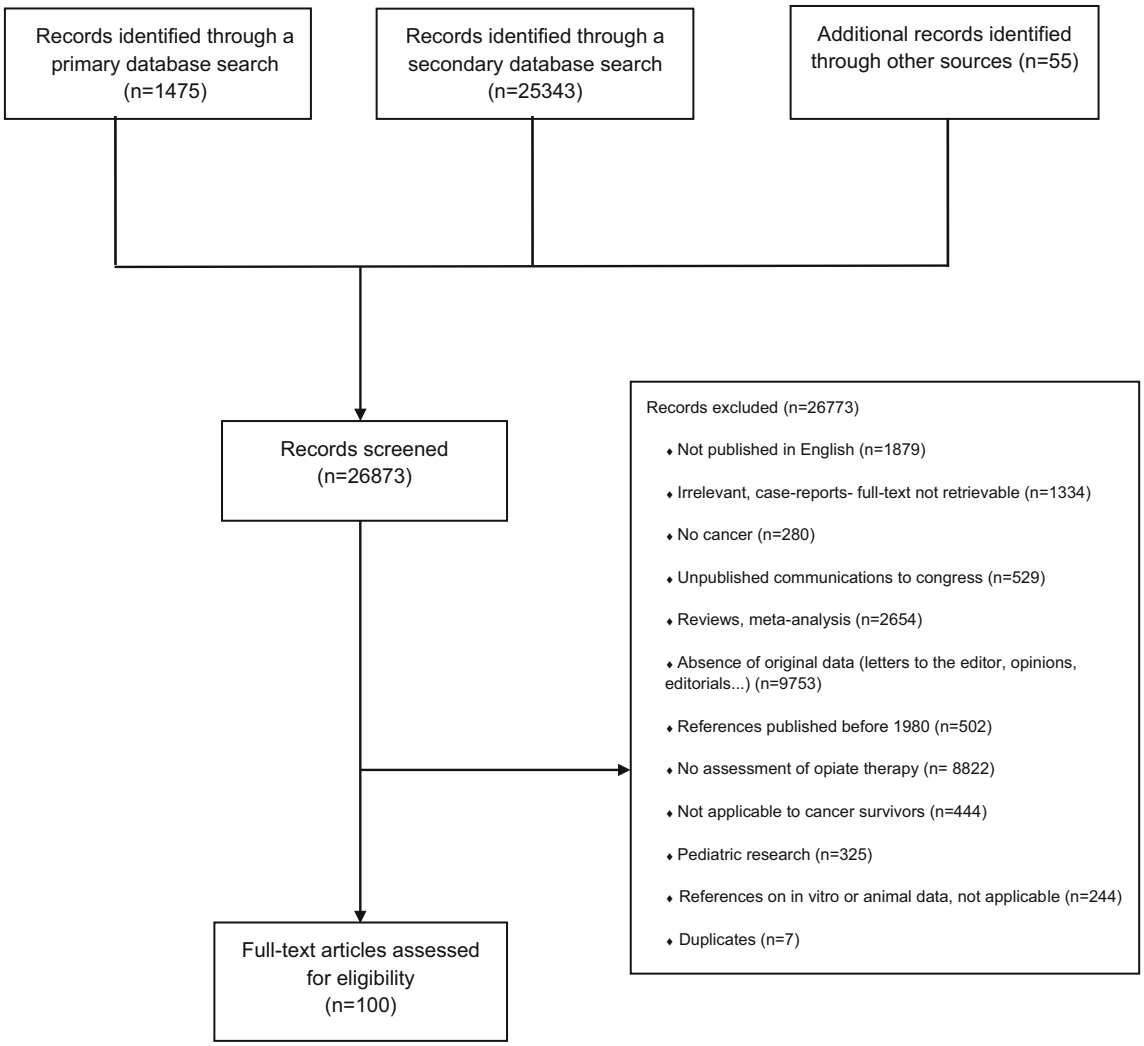

Fig. 1 Data review process

Table 2 Purpose of a literature review

Purpose	*n*	References
Immunosuppression or immune-related disorders	12	[28, 34, 43, 48, 51, 65, 73, 88, 93, 99, 103, 107]
Cardiovascular or neurologic complications	3	[57, 58, 60]
Endocrine disorders	11	[17, 22, 23, 39, 44, 47, 49, 53, 102, 110, 112]
Osteoporosis and bone health	5	[21, 37, 56, 100, 111]
Abuse or dependence	7	[15, 16, 24, 29, 31, 32, 36]
Overall survival	6	[18, 20, 30, 52, 62, 63]
Safety, toxicity and related topics	11	[27, 35, 38, 40–42, 46, 59, 108, 109, 113]
Efficacy and safety	2	[50, 114]
Quality of life	1	[55]
Return to work or employment	1	[45]
Cell kinetics or recurrence	41	[19, 25, 26, 54, 61, 64, 66–72, 74–87, 89–92, 94–98, 101, 104–106]

these drugs on long-term outcomes remain unknown. There are insufficient data to support their safety and efficacy for chronic pain, and a growing list of problems, ranging from addiction and abuse to death (see below), are consistently reported. Indeed, the vast majority of randomized trials in this field were designed to assess the effectiveness of opioid therapy within a limited time frame (1–6 months), and there is a clear paucity of large-scale studies evaluating opioid use over a longer time span [115]. This reflects the challenges of conducting the research for chronic pain with extended periods of observation that are required to substantiate these results.

The few publications available on this topic are non-interventional studies or the open-label phase of randomized trials in patients with non-malignant pain syndromes [38, 49, 50]. They allude to a limited benefit, including scarce functional improvement, for opioid therapy comparing alternative approaches and quality of life data are missing [46, 115, 116]. This lack of evidence is even more pronounced in long-term cancer survivors in whom treatment is often more complex, given the presence of physical and neuropsychological comorbidities (e.g., preexisting psychological conditions or endocrine disorders) that will impact treatment [14, 117]. Except for a few trials addressing chemotherapy-induced neuropathy, there are basically insufficient data to inform decisions about this population [118].

In contrast, other studies have concluded that chronic opioid therapy has marginal therapeutic benefit and may even delay functional recovery [119, 120]. Moreover, certain evidence points to poor treatment adherence in the long term. Most clinical trials, even those evaluating short-term effects, have consistently shown that a substantial number of patients discontinued treatment for different reasons. For instance, a meta-analysis designed to analyze the effectiveness and safety of opioids in chronic, non-cancer pain concluded that >56 % of patients discontinued medication after 7–24 months [121].

Long-term treatment safety

It is worth noting that, while opioids have been used in folk medicine for thousands of years, there is still reasonable doubt as to their long-term safety. Several reasons may account for this, such as the extended follow-up period needed to evaluate long-term side effects, the fact that toxicity often arises accidentally and unexpectedly, the heterogeneity of clinical manifestations, and pharmacological differences among opioids (affinity for the μ-opioid receptor, immediate- or controlled-release formulation, side effects, etc.). These medications may not act as a single, consistent family in terms of chronic toxicity. Causal evidence is scarce in the predominance of observational studies; basically, patients with worse baseline features are more likely to receive opiates. Although most studies have tried to minimize such selection bias, all may present residual confounding factors, which may explain the long-term side effects observed. Nevertheless, different reports that matched cases by disease and pain severity have pointed toward worse outcomes (health status, quality of life, or pain) for individuals on chronic opioid treatment, in comparison with other pharmacological therapies, rehabilitation programs, physical exercise, physiotherapy, or invasive techniques [45, 55, 63, 122, 123].

Furthermore, we know that the endogenous opioid system has many physiological functions beyond pain response modulation. Thus, endogenous opioid receptors are widely expressed in many tissues with pleiotropic functions (e.g., effects on chemokines and cell types involved in the immune response, the endocrine system, signal transduction systems, including mitogen-activated protein kinases or tumor suppressor genes such as p53) [43, 64]. The activation of these mechanisms continuously for years can lead to time-dependent side effects, such as endocrine disorders, immunological effects, neuroadaptation, etc. (Table 3).

Effects of prolonged opioid use on specific systems or organs in long-term cancer survivors

The immune system

The immune system is the cornerstone of our protection against pathogens, tumorigenesis, and tumor recurrence. When immunity is altered, it can have substantial negative impacts on the course of cancer. Chronic opioid treatment indirectly affects immunity by interfering with neuroendocrine pathways (such as, disruption of hypothalamic–pituitary–adrenal axis or other indirect pathways involving the central nervous system); in addition, it can directly impact target cells [28, 34, 43, 48, 51, 65, 73, 88, 93, 99, 103, 107]. The μ-opioid receptor is expressed in both macrophages and T lymphocytes, where it modulates the immune response [124, 125]. Likewise, chronic opioid administration decreases the proliferative activity of macrophages and lymphocyte progenitors [124]. Activation of the μ-opioid receptor is able to reduce acute inflammation by lowering proinflammatory cytokine production, which is mediated in part by B cell lymphoma-extra large (Bcl-xL) induction or nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) suppression, which trigger inflammation [99].

Opiates affect immune cell development, differentiation, and function, thereby raising the risk of bacterial infections in murine models [126]. This has been correlated to macrophage depletion via the induction of transforming growth

Table 3 Overview of long-term cancer survivors that potentially affect long-term opiate treatment

Location	Aspects to bear in mind in long-term cancer survivors
Central nervous system	Chemobrain in 30–50 % of patients treated with chemotherapy [143]
Peripheral nervous system	Chemotherapy-induced peripheral neuropathy is a frequent side effect of several cancer treatments [167]
Gastrointestinal	Gastrointestinal symptoms can occur as a result of physical damage or can be a sequela of certain anti-cancer treatments
Endocrine system	Azoospermia, amenorrhea, early ovarian failure, and sexual dysfunction are very common in cancer survivors [14, 136, 139]
Immune system	Higher incidence of infections and second tumors in this group. Possibility of damaging anti-tumor immune surveillance [128]
Bone	>27 % of the breast cancer survivors present osteoporosis. 18 and 55 % of elderly patients with prostate cancer will develop osteoporosis and osteopenia, respectively [21, 141]
Cardiovascular system	Higher risk of ischemic cardiopathy and cerebrovascular events, mainly as sequelae of previous cancer treatments [146]
Cell kinetics	μ-opioid receptor polymorphisms associated with decreased cancer-specific mortality in patients with breast cancer [18]
Addiction and abuse	A significant number of cancer patients (29 %) are classified as being at high risk for drug abuse [29]
Delay in returning to work	Only 63 % of long-term cancer survivors (range 24-94 %) are able to return to work [159]
Others	Hormone therapy; radiotherapy-induced xerostomia. Risk of interactions and polypharmacy

factor beta (TGF-β) mediated apoptosis [93]. Opioids have also been reported to interfere with monocyte and neutrophil chemotaxis and cause apoptosis in spleen cells [107]. While the effect on the general population may be transient, it can be more potent in immunodepressed patients, such as those who are positive for the human immunodeficiency virus (HIV). It has been proposed that morphine promotes HIV-1 proliferation inside human cells [88]. This may provide a molecular explanation for the role of opioids as cofactors in the pathogenesis of acquired immune deficiency syndrome (AIDS) in intravenous drug users.

The relevance of these findings in long-term cancer survivors, who typically present varying levels of immunosuppression [127], remains largely unexplored. A recent review evaluating the effects of opioids on the immune system in oncological patients has identified only five studies that address this issue. Although all the studies evaluated the effect of morphine on immunological endpoints, unfortunately none of them included clinical measures in their objectives [128]. Nonetheless, data from preclinical, healthy volunteers and surgical models suggested that different opioids influenced protective immune surveillance dissimilarly. Nevertheless, clinical practice recommendations could not be made on the basis of this inconclusive information. Well-designed clinical trials with large-sized samples are clearly required to inform physicians about the rational use of opioids in long-term cancer survivors. Other observational studies conducted in the post-operative setting have shown some beneficial effects on anti-tumor immunity with specific opioids such as tramadol [43, 103], so outcomes may depend on the particular molecule or its affinity for the μ-opioid receptor. The clinical impact of these observations for long-term cancer survivors is unclear, yet relevant given the increased incidence of infections and second tumors in this group [129–132]. Likewise, pain itself alters the immune system, thus converting patients on deficient antialgic therapy into the most vulnerable population.

Cell dynamics

An increasing number of studies, mainly conducted under in vitro cell culture conditions and in vivo in mice, suggest that opioids can alter cellular kinetics, and influence various cell programs including angiogenesis, proliferation, adhesion, invasion and metastases [19, 25, 26, 54, 61, 64, 66–72, 74–87, 89–92, 94–98, 101, 104–106]. However, at present, there is not enough evidence to hold that opioids have the ability to modify time to tumor progression or relapse-free survival. One study performed in 2000 patients diagnosed with breast cancer showed that μ-opioid receptor polymorphisms, known to confer morphine resistance, were associated with decreased breast cancer-specific mortality [18]. Unfortunately, there were insufficient data about the pattern of opioid use in this cohort. A second study revealed that oncological patients receiving intrathecal analgesics presented a better prognosis compared to those individuals receiving systemic morphine administration. This outcome must be interpreted cautiously. A speculative explanation for this finding could be the greater analgesic efficacy of small doses of morphine administered intrathecally, accompanied by less systemic exposure, resulting in a reduced incidence of side effects [114].

The opioid-growth factor receptor, also known as ζ-opioid receptor, contributes to regulating the cell cycle [64]. Also, a higher apoptotic rate in hepatocytes has been reported in the presence of opioids and even hepatitis or hepatic steatosis has been observed in patients on opioid treatment [109]. A particular effect on tumor cells under certain conditions cannot be ruled out. In contrast, epidemiological studies have failed to associate the use of chronic opioid therapy with a higher risk of developing cancer [62]. Finally, the Danish Breast Cancer Cooperative Group Registry, a cohort of 34,188 patients with localized breast cancer, did not find clinically relevant evidence of an association between opioid prescription and breast cancer relapse, regardless of the drug used, accumulated dose, and time to first administration [61].

Endocrine system

It is estimated that around 20 % of patients receiving long-term opioid therapy develop a significant endocrine dysfunction [49]. Chronic opioid use has been associated with the suppression of the hypothalamic–pituitary–adrenal and gonadal axes, with the subsequent decrease in luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estrogens, and cortisol. The main endocrine side effects are summarized in Table 4.

While these symptoms are more often described in heroin addicts or former addicts on methadone substitution therapy (certainly a peculiar population) [22, 133, 134], they have also been reported in patients taking opioids for chronic pain mainly caused by non-oncological processes [22], especially in those subjects with intrathecal analgesia [53]. Notably, despite the strong correlation, causality cannot be definitively confirmed based on these studies. Endocrine alterations depend on patients' clinical characteristics and even the diseases requiring opioid administration. For instance, one study looked at 40 patients with non-oncological chronic pain treated with opioids for more than 10 years. Interestingly, the level of C-reactive protein or the erythrocyte sedimentation rate were increased in 22 % of these individuals, suggesting active inflammatory hotspots that may be at the root of many endocrine disorders [49]. The problem is expected to worsen appreciably, because long-term cancer survivors very often experience preexisting endocrine alterations. For instance, several hormone deficits have been reported in 20–50 % of childhood cancer survivors, especially those who received radiotherapy, as well as in young women diagnosed with breast cancer who received alkylating agents and whose ovarian function was altered [135, 136]. Remarkably, the impact of chronic opioid therapy on these populations remains unknown.

Interestingly, data from recent human genome studies have shown that endogenous opioid receptors arose from gene duplication, from a primitive neurohormonal ancestral protein, joining the hormonal response to stress and nociceptive transmission [137]. This may be the reason why some interactions between pain transmission and stress hormone responses are common, even though both receptors have diverged in the human lineage and acquired tissue-specific functions. Evidence exists that administrating exogenous opioids long-term may still recapture these ancestral pathways with major clinical implications.

Hypogonadism and sexual dysfunction

Hypogonadism is often mentioned as being the most relevant side effect, since it may be clinically relevant (e.g., erectile dysfunction, infertility, loss of libido, amenorrhea, neurocognitive impairment, muscular mass loss, anemia, medullar suppression, or greater risk of cardiovascular events). Hypogonadism has consistently been reported to have lasting consequences for patients' quality of life, not least of all because it can increase vascular events and osteoporosis, leading to bone fracture and pain. In these patients, testosterone substitution therapy may be beneficial [138]. A further complicating factor may be chemotherapy-induced gonadotoxicity and premature ovarian failure, although more research is needed to confirm this. Some 15–30 % of male patients remain azoospermic several years after concluding chemotherapy regimens (alkylating agents, anthracyclines, etc.). It is also well known that

Table 4 Summary of endocrine effects related to chronic opioid therapy

Glands	Possible effect
Hypothalamic–pituitary–gonadal axis (hypogonadism)	Sexual and erectile dysfunction, infertility, decreased libido, amenorrhea, anxiety, fatigue, depression
Hypothalamic–pituitary–adrenal axis (hypocortisolism)	Fatigue, hypotension, osteoporosis, loss of muscular mass, cognitive impairment
Prolactin concentration increased	Sexual dysfunction, galactorrhea, amenorrhea
Growth hormone suppression	Anxiety, emotional instability, fatigue
Thyroid	Not described as yet; clinical consequences can include weight loss, fatigue, or depression

chemotherapy can induce amenorrhea and early ovarian failure [136]. Likewise, breast and prostate cancer patients normally receive hormone therapy (antiandrogens, gonadotropin-releasing hormone analogues, tamoxifen, etc.) that compounds this problem even more [136].

Furthermore, chronic opioid therapy may be one of the most common causes of sexual dysfunction in long-term cancer survivors, affecting up to 50 % of all subjects. Indeed, a case–control report assessing symptomatic hypogonadism in male survivors of cancer found that the vast majority of patients on chronic opioid therapy (≥1 year) exhibited clinical hypogonadism [90 %; 95 % confidence interval (CI) 65–98 %], accompanied by higher rates of sexual dysfunction, fatigue, and depression [139]. In contrast, far fewer patients without chronic exposure to opioids presented insufficient testosterone secretion (40 %; 95 % CI 19–64 %). While this study did not control for the severity of pain, which, in itself can affect sexual hormones, the authors defended their conclusions on the grounds that the same effect had been described in former intravenous drug users who were on methadone substitution therapy and who reported no pain.

Other endocrine effects

An increased concentration of prolactin has also been noted with unknown consequences. However, it could account for episodes of galactorrhea or irregular menstrual cycles in women and diminished libido or erectile dysfunction in men. Growth hormone down-regulation has also been reported [140], though its clinical significance remains unexplained. Finally, decreased cortisol has also been identified, which can translate into asthenia, hypotension, osteoporosis, cardiovascular disturbances, neurocognitive failure, labor issues, and poor quality of life, although its true clinical impact has yet to be elucidated. Thus far, thyroid hormone dysfunctions have not been reported.

Bone health in long-term cancer survivors

Cancer and its treatments can have major effects on bone health. Over 27 % of breast cancer survivors present osteoporosis [21]. In men, 18 % of patients >70 years old with prostate cancer who receive androgen deprivation therapy will develop osteoporosis and 55 % of them will develop osteopenia [141]. Loss of bone mineral density can be further complicated by long-term opioid exposure. This can be indirectly explained by hypogonadism and directly, by effects on bone remodeling (e.g., interfering with osteoblast activity) [142]. The risk seems to depend on dosage, the type of opioid, and short-acting opioid exposure. Opioid osteoporotic potential can differ [100, 110]. Chronic opioid therapy has also been associated with increased risk of falls and fractures, [hazard ratio (HR) 3.5–6.9] when analyzed against non-steroidal anti-inflammatory drugs [37, 142].

Neurological complications

Cancer survivors often display varying degrees of chronic neurologic impairment referred to as "chemobrain", consisting of memory alterations, learning difficulties, and impaired concentration, reasoning, executive function, or visual skills. Since this syndrome has been described almost exclusively in women diagnosed with breast cancer, its actual incidence has not been established. Chemobrain is thought to be present in 30–50 % of chemotherapy patients [143]. Furthermore, chronic or high doses of opioids or their metabolites (e.g., morphine-3-glucuronide or hydromorphone-3-glucuronide) have proven neurotoxicity, which may explain the cognitive impairment seen in substance abusers. A meta-analysis indicates that chronic opioid exposure is associated with deficits across a variety of neuropsychological domains, including working memory, verbal fluency, as well as higher impulsivity, although some neurocognitive deficits may be recoverable through neuronal plasticity [144]. The net effect is probably complex, and needs further exploration, since μ-opioid receptor pathways also activate different mechanisms affecting neural survival and plasticity [89].

Cardiopulmonary effects of chronic opioid treatment

Long-term cancer survivors are at higher risk for ischemic cardiopathy and cerebrovascular events, compared to the general population, primarily as treatment sequelae. This is especially true for patients with Hodgkin lymphoma treated with supradiaphragmatic radiotherapy, testicle cancer, or left breast cancer patients [145–148]. Several cytotoxic agents are known to affect endothelial cells.

The impact of long-term opioid treatment on this population is not clear, as most studies have been carried out in patients without cancer. Cardiovascular disturbances have been reported as possibly associated with chronic opioid therapy [149, 150], which may be partially and indirectly attributed to hypogonadism. Thus, this is another clinical situation of mutual feedback. Indeed, testosterone appears to inhibit proinflammatory cytokine production, which may mediate in the formation of coronary atheromatous plaques. Case–control studies report a slight increase in acute myocardial infarction [odds ratio (OR) 1.19–1.37] in patients who received prolonged opioid therapy [60, 149].

Finally, opioids have also been related to sleep apnea, with an estimated prevalence of 24 % among chronic

consumers, especially those who use daily oral morphine equivalent doses >200 mg [151]. The relevance this has on long-term cancer survivors awaits examination.

General concerns regarding the chronic use of opioids in long-term cancer survivors

Addiction and abuse in long-term cancer survivors

While "drug abuse" and "addiction" tend to be used interchangeably, they have actually different meanings. Substance abuse is a more general concept that typically refers to a harmful and inappropriate use of medications. Drug abuse may eventually lead to addiction, defined as a chronic mental disorder that is characterized by compulsive drug seeking and use, despite harmful consequences.

Most studies addressing addiction and abuse contemplated in this review are not specific to oncological patients. Nonetheless, they have been included here, since some of the epidemiological and risk factor aspects are characteristic to this patient population. Our review has revealed the need for prospective research in this field.

Epidemiological studies in chronic pain patients have estimated rates of drug abuse, dependence, and addiction to be in the range of 3–19 % [152]. However, it is generally accepted that patients with active cancer and chronic pain syndromes (CPS) have a very low risk for drug abuse or addiction. Still, this conclusion has not been proven to be germane to long-term cancer survivors [153].

Opioid abuse behaviors (taking large amounts, craving, prescription-pill abuse, using opioids in a fashion that affects the fulfillment of personal obligations and responsibilities, etc.) constitute a different, yet related point. Community-based studies have estimated 4–26 % rates of opioid overprescription [154]. Chronic opioid treatment is more often prescribed for individuals with more pain localizations, more systemic diseases, or more psychiatric disturbances [155]. This last point can potentially determine the onset of abusive behaviors, since higher doses of opioids are frequently reported in patients with psychological disturbances [36].

Long-term cancer survivors suffer from several adjustment disorders, including fear and anxiety (27–40 %), difficulties returning to work, dependence, sexual dysfunction, altered social skills, self-esteem issues, and post-traumatic stress (5–15 %) [117, 156]. In a meta-analysis of 44 studies on the prevalence of mood disorders in patients diagnosed with cancer at least 2 years previously, the authors found anxiety among long-term cancer survivors to be around 18 %, compared to 14 % in the general population ($p = 0.003$) [117]. In fact, psychological distress has been related to drug abuse in earlier reports. Indeed, when cancer patients were evaluated with specific scales, such as the Screener and Opioid Assessment for Patients with Pain, Short Form (SOAPP-SF), a significant number (29 %) were classified as being at high risk for drug abuse [29]. Interestingly, patients in the high-risk category were younger and had high levels of anxiety or depression disorders. Finally, certain personality traits may also increase the risk of substance abuse and addiction [157].

All-cause mortality and chronic opioid use

Our bibliographic review has not uncovered any specific references about mortality related to opioid use in long-term cancer survivors. We feel it is a priority that must be addressed. The extrapolation of data from the general population suggests that it can have an enormous impact on the long-term cancer survivor. For example, a population-based cohort of 13,127 adults who participated in the Danish Health Interview Surveys in 2000 or 2005 proved that all-cause mortality was 1.7 times higher for patients on chronic opioid therapy, without detecting specific causes of death [62]. Chronic opioid use correlated with higher rates of injuries, toxicity, and overdose, translating into more hospitalizations. Even though comparative analyses are inconclusive, specific risks may still depend on the particular medication being used (morphine, fentanyl, oxycodone, etc.) [27, 30]. A retrospective observational cohort drawn from the Department of Veterans Affairs (VA) healthcare databases detected no evidence of excess all-cause mortality among VA individuals who received methadone compared to those who were treated with long-acting morphine, although it was recommended that randomized trials be conducted to understand and analyze the safety of long-acting opioids [30]. Another epidemiological study carried out using Medicaid administrative claims data showed a slight benefit in terms of toxicity for prolonged-release oxycodone in comparison to controlled-release morphine. Fentanyl and methadone also correlated with more adverse events than controlled-release morphine in patients with non-oncological pain [27]. One possible explanation for the discrepancy of methadone's safety between outcomes from the Medicaid and VA cohorts may lie in the management and surveillance differences of each healthcare program. These data are mostly from non-oncological patients and it is unclear if the findings are applicable to long-term cancer survivors. We believe that this highlights the need for specialized teams to treat this kind of patient from an integrative perspective.

Other social or occupational effects

Delaying long-term survivors' return to work may be another undesirable effect of chronic opioid use. In patients

with occupational injuries, the probability of chronic work loss seems to be higher in those who received potent opioids [45, 123]. A systematic review of several studies performed between 1966 and 2008 found that cancer survivors were frequently unemployed, especially if they had been diagnosed with breast, gastrointestinal, or gynecological tumors [158]. Another systematic review of 64 studies published between 2000 and 2009 discovered that a mere 63 % of long-term cancer survivors (range 24–94 %) were able to go back to their jobs, although the impediments to their return were, logically, varied. Median duration of sick leave was 151 days [159].

Clinical practice recommendations for chronic opioid therapy

Clinical guidelines endorse the use of chronic opioid therapy for patients presenting severe pain when alternate approaches have failed [160]. However, the source of pain or inflammation should be acted on directly, favoring therapies that can both restore original functions and rehabilitate. The aim of opioid treatment is to accelerate this recovery. Alternatives such as physical exercise, cognitive therapies, physiotherapy, adjuvant drugs (e.g., antidepressants or anticonvulsants), or invasive techniques (such as kyphoplasty or nerve blocks) should also be weighed. Should these therapies fail, chronic opioid treatment with well-defined goals can ease these patients' suffering. The pros and cons must be balanced and both doctors' and patients' agreement should be obtained for an adequate follow-up. The best way to minimize the risk of addiction and other untoward effects is to comply with clinical practice guidelines [160, 161]. Table 5 summarizes recommendations for patient selection, procedures, and follow-up.

Patient selection for chronic opioid therapy

The first step is to select those patients for whom the risk/benefit ratio is most favorable. The precautionary principle must be the deciding factor. Oncologists or other health care providers should exercise extreme care when prescribing chronic opioid treatment to individuals diagnosed with psychiatric disorders, behavioral issues, or who have a history of substance abuse [152, 154]. It is worth noting that clinical trial exclusion criteria have tended to comprise psychiatric comorbidity or drug abuse history, despite the fact that prescribing opioids to these individuals may be inevitable in daily practice. Cancer survivors with a history of drug abuse or addiction can benefit from opioid pain medications if monitored correctly [162]. In such

Table 5 Recommendations for long-term cancer survivors on chronic opioid therapy

Main aspects	Attitude and objectives of chronic opioid therapy
General	Identify type and pathophysiology of pain
	Rule out tumor relapse
	Treat the source of pain, favoring therapies that can both restore original functions and also rehabilitate
	Consider other alternatives, such as physical exercise, cognitive therapies, physiotherapy, adjuvant drugs, or invasive techniques
	Treat patients on an individual basis, in appropriate, controlled environments with specific, objective goals
Dosage and administration	Prolonged-release formulations are recommended (less risk of addiction)
	No clear evidence that any opioid is better than another
	Try to achieve main goals at low, intermittent opioid doses (preferably <90 mg/day morphine or equivalent for ≥3 months)
	Avoid or minimize high doses or long-term continuous exposure
Monitoring	Recommended follow-up visits every 3–6 months
	In patients with increasing pain, eliminate possibility of a tumor relapse; consider addiction, psychological disturbances, or opioid-induced hyperalgesia
	Avoid sudden withdrawal (abstinence syndrome)
	Evaluate opioid rotation if needed (e.g., if the patient needs more than 180 mg/day morphine or equivalent)
Surveillance	Test for endocrine alterations (prolactin, LH, FSH, testosterone, estrogens, cortisol, and ACTH) in patients with symptoms
	Manage side effects associated with chronic use. Substitute therapy with low-dose hydrocortisone or testosterone can help patients with opioid-induced endocrine disturbances
	If effects suspected related to chronic opioid therapy, rotation to another molecule with a lower affinity for μ-opioid receptors can help
	Slowly taper dosage if withdrawal is necessary

situations, negotiating goals (quality of life, preserving specific functions, etc.) can be contemplated together with close monitoring (e.g., providing the indispensable number of prescriptions for pain medication, counting pills, drug screens, and careful prescription documentation). Therefore, no contraindication is "absolute" in long-term cancer survivors suffering pain; however, the mutual feedbacks between common cancer survivors' preexisting conditions and chronic opioid exposure must be emphasized.

Chronic opioid therapy: dosage and administration

Evidence of controlled or prolonged-release opiates' greater safety is limited [163, 164]. Even so, these formulations are preferable, given the conceivably lower risk for addiction or abuse [160].

Nothing points to any one opioid being superior in terms of safety or efficacy [17]. One study showed that tapentadol, a centrally acting analgesic with dual mechanism of action (weak affinity for the μ-opioid receptor and norepinephrine reuptake inhibition), may be less toxic for sexual hormones, especially testosterone [110], although this observation requires further confirmation. Osteoporosis has also been reported to be dependent on the opiate, treatment duration, dose, patient age, and comorbidities. One preclinical study has detected lower risk of osteoporosis with tramadol for chronic pain versus morphine or fentanyl, perhaps because the former is a much weaker μ-opioid receptor agonist, albeit further clinical trials are needed to confirm these results and assess their long-term impact [100]. Other studies suggest that methadone or oxycodone might be safer than morphine in certain aspects, such as opioid-related adverse events, hospitalizations, risk of death, etc., in patients with largely non-oncological pain [27, 30]. Nonetheless, all these data come from uncontrolled epidemiological series and must be taken cautiously. No recommendations for clinical practice can be made on this basis.

A regime often recommended in the literature is the use of low, intermittent doses (<90 mg/day morphine or equivalent, for no more than 3 months). In contrast, higher, continuous doses tend to exhibit scant effectiveness [35, 165]. Theoretically, long-term cancer survivors should not receive dose escalations for worsening pain. If this happens, look for the cause. If pain increases or there is a new physical symptom, all necessary testing should be conducted to rule out tumor relapse. If the source of pain cannot be uncovered, the possibility of drug addiction, a new psychological disturbance, or opioid-induced hyperalgesia (in which case, higher doses of opioids may paradoxically worsen the situation) should all be considered [102]. If rescue opiates are needed, it is reasonable that short-acting opioids be administered, as for non-oncological patients. However, there is a paucity of evidence in this regard.

If intolerable side effects develop or higher doses are required, opioid rotation (switching from one opiate to another) should be considered. Opioid switching has proven to be as effective as dose escalation with fewer adverse events. While there is no fixed threshold, opioid rotation is typically considered a good alternative when more than 180 mg/day of oral morphine or equivalent are needed.

We must underscore that chronic opioid therapy should not be suspended abruptly to avoid withdrawal syndrome. Gradually tapering by 10 % every 2–4 months is recommended; hence, it may take months to discontinue opioid-based therapy. On the contrary, some patients may need a maintenance approach to avoid the negative effects of a sudden withdrawal [166].

Finally, the risk of harm from long-term polypharmacy must be assessed. One of the biggest concerns in clinical practice is polymedication, especially in the elderly, in whom benzodiazepines can set off opioid-related side effects. A retrospective study of the New York metropolitan area studied individuals over 65 years old. They found a 5 % rate of hospitalizations secondary to opioid-related adverse events [41]. Nonetheless, in that study, chronic opioid therapy was used mainly in non-oncological patients with a median age of 82 years.

Monitoring and follow-up

Close monitoring is recommended for long-term cancer survivors on chronic opioid therapy. Ideally, oncologists or other physicians experienced in cancer supportive care conduct follow-up in collaboration with a Pain Unit. Visits should be planned every 3–6 months during opioid treatment.

Despite the lack of direct clinical evidence regarding possible strategies to minimize adverse events [164], substitutive therapy has been reported to possibly palliate the effect of some opioid-induced endocrine dysfunctions. A small, double-blind, randomized pilot study showed that hormone replacement therapy with hydrocortisone improved vitality and pain compared with placebo [112]. This might account for the benefit from adding steroids, even at low doses, to regular analgesic schemes [112]. In a small study, testosterone was found to ease the effects of intrathecal opioids on testosterone levels and bone mineral density [111]. We, therefore, recommend periodic clinical surveillance to detect symptoms of endocrine disorders. Additional tests are needed in these cases, including blood testosterone, estrogens, sex hormone-binding protein (SHBP), cortisol, adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) [140]. No standard treatment exists if these

disorders are present, given the modest evidence. A meticulous clinical history must be taken to elucidate if the analytical abnormalities truly translate into clinical alterations. If a symptomatic patient is diagnosed and there is a strong suspicion that opioid therapy is the main cause, opioid rotation to other molecule with a lower affinity for μ-opioid receptors would be sensible [140]. Alternatively, pharmacological or non-pharmacological alternatives (psychosocial interventions, invasive therapies, etc.) can be sought to reduce the opioid dose. Other possible causes must be ruled out if hypogonadism is discovered. Bone densitometry can also be helpful. If testosterone substitution therapy is chosen [111], possible adverse events (such as prostate hypertrophy) should be accurately monitored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Not applicable.

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