


# Less Well-Known Consequences of the Long-Term Use of Opioid Analgesics: A Comprehensive Literature Review

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**Background:** The adverse effects of short-term opioid analgesics are well known and acknowledged; however, the spectrum of the sequelae of long-term use seems less clear. Some effects may remain undetected but still have the potential to cause harm and reduce patients' quality of life.

**Objective:** To review the literature on the adverse effects of long-term opioid therapy.

**Methods:** We performed a quasi-systematic search, analyzing articles published in the MEDLINE database between January 2000 and March 2021 that identified adverse effects of opioids used for chronic pain treatment.

**Results:** Growing evidence indicates that there are multiple serious adverse effects of opioid treatment. Long-term opioid use may have significant effects on the endocrine, immune, cardiovascular, respiratory, gastrointestinal, and neural systems. Studies show that long-term opioid treatment increases the risk of fractures, infections, cardiovascular complications, sleep-disordered breathing, bowel dysfunction, overdose, and mortality. Opioids may potentially affect cancer development. Most consequences of the long-term use of opioids have been identified in studies of patients with non-malignant pain.

**Conclusion:** Studies indicate that long-term use of opioids increases the risk of drug-related events in a significant number of patients. Clinicians should be aware of these complications associated with prescribing opioids, discuss them with patients, prevent complications, if possible, and diagnose them early and manage adequately. More human studies are needed to assess the risk, including trials with individual opioids, because they have different adverse effect profiles.

**Keywords:** opioids, chronic pain, adverse effects, long-term treatment, safe therapy

## Introduction

Opioids are widely used for the treatment of pain. Their consumption has increased significantly in the last two decades, and they are now used not only for advanced cancer patients but also for those in the earlier stages of the disease and in many individuals with pain due to non-malignant diseases. Survival rates for patients with cancer have also improved notably, and many of these cancer survivors still need opioid treatment. Although the adverse effects of opioids used for a short time are well known and acknowledged, the sequelae of the long-term use of these drugs are less known and understood by many clinicians.<sup>1–6</sup> This issue gains special importance in the view of growing need for adequate pain treatment in aging societies in developed countries, worldwide undertreatment of pain and coexisting problems of

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opioid crises in some regions of the world in the recent decade.<sup>7–9</sup> This manuscript will highlight current knowledge in the area of the long-term adverse effects of opioids used for pain treatment.

## Materials and Methods

We performed a quasi-systematic search, analyzing papers published between January 2000 and March 2021 in the MEDLINE database identified after typing a combination of “opioid, adverse effects, long-term therapy, chronic pain, hypogonadism, endocrinopathies, fractures, immunomodulation, immunosuppression, cancer development, cancer growth, infections, cardiovascular events, bowel dysfunction, narcotic bowel syndrome, sleep-disordered breathing, overdose, death”. From a plethora of search results, we selected papers that examined the use of opioids for chronic non-cancer and cancer pain, including pain induced by antitumor therapy. We referred “long-term” opioid therapy to the treatment of chronic pain, lasting longer than 3 months. We excluded trials investigating extra-medical use of opioids, non-human studies and selected randomized controlled trials (RCTs), case–control studies, cohort studies, systematic reviews and meta-analyses. However, if such trials were not found, we referred to preclinical studies in order to present important issues related to opioid use which needs further clinical investigations.

## Results

The review of the literature indicates that opioids used for the treatment of chronic pain may cause a varied spectrum of potentially serious adverse effects. Opioids have significant effects on the endocrine, immune, cardiovascular, respiratory, gastrointestinal and neural systems.<sup>10–20</sup> They increase the risk of fractures, infections, cardiovascular complications (including myocardial infarction), sleep disturbances and sleep-disordered breathing, bowel dysfunction, overdose and mortality due to opioid overdose or other causes.<sup>15–18,21–27</sup> Opioids may potentially affect cancer development.<sup>28–30</sup> Most adverse effects of the long-term use of opioid analgesics have been identified in studies of patients with non-malignant pain. Some adverse effects have been studied only in animal models and their importance in humans has not been fully confirmed.

## Endocrine Effects

Most publications on opioid-induced endocrinopathies concern hypogonadism (opioid-induced hypogonadism, OIH).<sup>10–13,31–33</sup> Opioids inhibit the hypothalamic-pituitary-

gonadal (HPG) axis by acting primarily on mu opioid receptors in the hypothalamus. They inhibit the pulsatile secretion of gonadotropin-releasing hormone from the hypothalamus and decrease the secretion of luteinizing hormone and to a lesser extent follicle-stimulating hormone from the pituitary gland, which results in a fall in testosterone and estradiol release by the gonads.<sup>31,34–36</sup> The symptoms of sex hormone deficiency may manifest as loss of libido, impotence in males, menstrual cycle disturbance in women and infertility. Opioids may also increase prolactin levels and be responsible for galactorrhea and gynecomastia.<sup>31,34</sup> All these symptoms may be accompanied by the loss of energy and depression.<sup>3,32,35</sup> Of note, hypogonadism may be associated with increased sensitivity to pain and poor pain control.<sup>36–40</sup> Long-term use of opioids may result in decreased muscle mass and bone loss.<sup>37,41</sup>

Decreased levels of sex hormones after opioid use were first described in subjects abusing heroin and during methadone maintenance.<sup>42,43</sup> Most papers concerning OIH in patients treated for pain have been conducted with men, and there are many fewer reports concerning the effects of opioids on the endocrine glands in women.<sup>3,10–12,36,37,44–46</sup> According to a number of analyses, OIH occurs in 19–86% of men using opioids for chronic non-malignant pain depending on the criteria of hypogonadism applied, opioid type, duration of use and the characteristics of population.<sup>32,37,47–49</sup> According to a systematic review clinical symptoms of hypogonadism (oligo/amenorrhea) were present in 23–81% of women aged 18–55 years treated with opioids for chronic non-malignant pain for 1 month or longer.<sup>11</sup> An association between opioids and hypogonadism was also demonstrated in cancer patients and cancer survivors.<sup>13,35,49,50</sup> For example, 64% of patients with advanced cancer had a low level of testosterone, which correlated with the Hospital Anxiety and Depression Scores.<sup>35</sup> Hypogonadism was also found in 18 out of 20 (90%) male cancer survivors treated with opioids for over 1 year (compared to 40% for the control group).<sup>49</sup>

The degree of hormonal deficiency may depend on the individual opioid used. In a retrospective cohort analysis, the odds of androgen deficiency were higher in men using fentanyl, methadone or oxycodone as compared with individuals using hydrocodone.<sup>51</sup> Some reports indicated that buprenorphine and tapentadol may have less of an effect on the levels of sex hormones.<sup>11,37,52–55</sup> The risk of OIH is higher with higher opioid doses (>100 mg morphine equivalent daily dose, MEDD) and the use of long-acting opioids as compared to short-acting.<sup>12,13,37,47,50,51,56–58</sup> Most probably, when short-acting opioids are used,

pulsatile hormone release takes place between the doses and thus prevents hypogonadism.<sup>51,57</sup>

Supplementation with sex hormones may improve sexual functioning and should be considered under close specialist supervision whenever opioid dose reduction or opioid cessation is not feasible.<sup>3,31,59</sup> Of interest, hormone supplementation may reverse hyperalgesia and improve pain control in patients treated with opioids.<sup>37,38,60,61</sup>

In addition to suppression of the HPG axis, opioids can inhibit the hypothalamic–pituitary–adrenal (HPA) axis through inhibition of corticotropin-releasing hormone, resulting in decreased adrenocorticotropin (ACTH) release.<sup>3,62,63</sup> Both short-term and long-term use of opioids for pain treatment were demonstrated to cause hypocortisolism that in some cases manifested as adrenal crisis.<sup>46,48,63–69</sup> It should be borne in mind that cortisol levels are increased in patients suffering pain, which may counteract opioid-induced hypocortisolism. Opioids may, however, disturb ACTH and cortisol diurnal rhythms and decrease the adrenal response to hypophyseal stimulation.<sup>66,68–70</sup> Reports show that cortisol concentrations below normal levels occur in 9–29% of subjects using opioids in long-term therapy.<sup>48,62,71</sup> Adrenal insufficiency was described after administration of morphine, diamorphine, hydromorphone, fentanyl, tramadol and loperamide.<sup>3,62,63</sup>

Opioid therapy may also cause hormonal changes of less clinical significance. The data regarding alterations in growth hormone and thyroid-stimulating hormone secretion remain inconclusive.<sup>3,32,46,48,50</sup>

## Osteoporosis and Increased Fracture Risk

Decreased bone density in patients treated with opioids and increased risk of fractures have been well documented.<sup>3,72–75</sup> In patients using long-term opioids, the prevalence of osteopenia and osteoporosis may reach 50% and 20%, respectively.<sup>3,41,58</sup> These phenomena can be related to hypogonadism (see above), but also to the  $\mu$ -receptor-related inhibition of osteoblast activity and interference of opioids with bone turnover.<sup>72</sup>

A meta-analysis of 18 cohort or case–control studies concerning patients with chronic non-cancer pain showed that in patients treated for pain with opioids, the overall risk of fractures increased by about 80%.<sup>22</sup> The higher risk of fractures has been confirmed for a number of opioids (morphine, oxycodone, fentanyl, tramadol and codeine, among others) and demonstrated to be greater with higher

doses and the use of short-acting opioids.<sup>21,72,76,77</sup> Surprisingly, according to some studies, the risk of fractures is highest in the first 2 to 3 weeks of treatment (a more than six-fold increase in the risk), which suggests association of these events with falls due to sedation and dizziness caused initially by opioids.<sup>21,78</sup> However, osteopenia and osteoporosis may be the cause of bone fractures that occur later in the course of the treatment.<sup>3,72,77</sup>

## Immunomodulatory Effects of Opioids

Opioids influence cellular and humoral immunity in a complex way. During the course of the inflammatory process, endogenous opioids are released by activated leucocytes and play the role of mediators in the immune system, influencing the proliferation of T lymphocytes and regulating the activity of natural killer (NK) cells, the synthesis of antibodies and the phagocytic function of macrophages.<sup>79–81</sup> Most publications relating to the immunomodulatory effect of exogenous opioids were preclinical experiments conducted with morphine.<sup>82</sup> Morphine may inhibit NK cell cytotoxicity, the differentiation and function of macrophages and progenitor lymphatic cells, chemotactic and phagocytic activity of granulocytes and monocytes, proliferation of T and B cells and the expression of pro-inflammatory cytokines.<sup>14,79,80</sup> Experimental studies indicate that individual opioids differ in their effects on the immune system, and the effect is also related to the dose used and duration of treatment.<sup>82–84</sup> Morphine was demonstrated to have a strong immunosuppressive effect.<sup>14,81,82,85</sup> Fentanyl showed a dual effect on immune system. Most studies indicated strong immunosuppressive effect of fentanyl similar to that of morphine. Interestingly, some experiments in animal models showed disappearance of fentanyl-induced immunosuppression after a few days of continuous use of this drug, suggesting development of tolerance to this effect.<sup>86,87</sup> Large fentanyl doses administered perioperatively in human studies (75–100  $\mu\text{g}/\text{kg}$ ) caused prolonged suppression of NK cell cytotoxicity as compared to low doses (1–5  $\mu\text{g}/\text{kg}$ ).<sup>84</sup> In contrast, investigations assessing the effect of intravenous fentanyl in healthy volunteers showed increased cytotoxicity of NK cells related to an increase in the proportion of this fraction of cells in the circulation (and not their activity).<sup>88,89</sup> Oxycodone and methadone demonstrated a weak effect on the immune system.<sup>80–82,90</sup> Buprenorphine was shown to have a minor or no effect.<sup>86,91,92</sup> In contrast to most opioids, tramadol appears to have intrinsic immunostimulatory properties, which may be related to its serotonergic activity.<sup>93</sup> In experimental studies, tramadol enhanced NK cytotoxicity, proliferation of

lymphocytes and cytokine production but had no effect on phagocytic capacity of polymorphonuclear cells and monocytes and prevented surgery-induced suppression of NK cell activity.<sup>79,80,82,94–96</sup>

## Influence on Neoplastic Transformation

Multiple experimental studies show that opioids can promote the processes of angiogenesis, proliferation, adhesion, infiltration and the formation of distant metastases.<sup>28,29,97</sup> These effects are diverse and depend on the individual opioid and the doses used.<sup>29,30,95,98</sup> In line with these observations, some investigations demonstrated that the opioid antagonist methylnaltrexone (MNTX) may inhibit tumor growth and metastatic behaviors in certain cancers.<sup>98,99</sup> In contrast to the above observations, some experiments demonstrated a potentially protective effect of some opioids in cancer. For example, methadone was shown to induce apoptosis of leukemia cells and increase sensitivity of some cancer cells to chemotherapy.<sup>100–102</sup> Also morphine, fentanyl and oxycodone were shown to exert proapoptotic effects on cancer cells and inhibit metastatic mechanisms in experimental models.<sup>103–107</sup>

This preclinical evidence confirms that opioids may modify cancer progression, although whether the balance of effects favors increased or decreased risk of cancer progression in individual situations remains unclear. In recent years, multiple publications in humans aiming to define the association of the use of opioids and cancer development have been published. Their interpretation is, however, difficult and definite answers to these concerns cannot be given so far. Different outcomes in these experiments reflect multiple contributing factors and their limitations. The most important of these studies are summarized below.

Mu opioid receptors were demonstrated to be over-expressed in several human malignancies and their higher expression was demonstrated to be associated with cancer progression and a shorter survival.<sup>28,108–111</sup> In line with these observations, a longer survival after mastectomy in women with polymorphism of single nucleotide A118G, which determines a lower sensitivity to morphine, was concluded; however, the study did not provide information about opioid use by the patients, which is its important limitation.<sup>112</sup>

The most abundant data on cancer promotion concern the impact of analgesia used during tumor resection. Many, but not all, authors indicated that opioid-sparing regional

techniques may be associated with a favorable outcome as compared to systemic analgesia.<sup>113–117</sup> These studies are criticized, however, due to methodological limitations and the fact that multiple other coexisting factors (such as surgery, pain, and some anesthetic drugs used, among others) may cause immunosuppression in this clinical setting.<sup>115,118–120</sup> In a recent multicenter RCT including over 2000 women having potentially curative primary breast cancer resection, regional anesthesia-analgesia did not reduce breast cancer recurrence compared with general anesthesia and systemic opioids.<sup>121</sup>

An association between opioid use and survival was evaluated in a number of other studies in cancer patients, but most were stated to be inconclusive.<sup>109,122–128</sup> According to a recent systematic review including 28 studies with cancer patients, existing evidence indicates that cancer-related pain management with the use of opioids is associated with poor overall survival (OS) in advanced cancer patients (but not progression-free survival, PFS). Postoperative analgesia had poor effect on PFS (but not OS) and intraoperative opioids use was not demonstrated to be associated with survival.<sup>123</sup> An interesting conclusion was presented in a secondary analysis of a prospective study including 1404 patients with advanced cancer.<sup>124</sup> This study demonstrated association between opioid use and decreased survival; however, the relationship weakened in a subgroup analysis adjusting for C-reactive protein. The authors raise an interesting hypothesis that survival in these patients may be partly related to tumor-related inflammation causing increased pain and the need to administer opioids.<sup>124</sup> Tumor-related inflammation is a factor associated with cancer cachexia, which by itself can influence prognosis and survival.<sup>129,130</sup>

Interesting results were also obtained in a secondary analysis of data from two RCTs in advanced cancer patients with opioid-induced constipation treated with the opioid antagonist MNTX. A significant increase in overall survival was found in these patients compared to the placebo group.<sup>131</sup> Assessing patient survival was not a primary aim of the study, however, which limits its significance.

The risk of developing cancer and cancer mortality was evaluated in a prospective manner in over 13,000 individuals with chronic non-cancer pain followed for up to 10 years. No difference in the risk of developing cancer and cancer mortality was found between long-term opioid users and individuals without chronic pain.<sup>132</sup> When interpreting this data, one has to consider the long timeline of cancer development. Ten years of observation, however

long, may not be sufficient to assess the full risk. Further epidemiological prospective long-term trials in individuals with chronic non-malignant pain are needed.

## Infections

Another potential consequence of opioid-related immunosuppression includes increased susceptibility to infections. Increased risk of these serious complications has been revealed in a number of epidemiological studies.<sup>23,24,133–135</sup> For example, opioid use was associated with a 38% higher risk of community-acquired pneumonia and a more than 60% increased risk of invasive pneumococcal diseases.<sup>23,133</sup> In a study of patients with rheumatoid arthritis, serious infections necessitating hospital admission appeared 40% more often during periods of current opioid use compared to periods of non-use.<sup>134</sup> The incidence rate of infections in these studies was higher when long-acting opioids with stronger immunosuppressive properties were used in higher doses.<sup>23,24,133,134</sup> Interestingly, the risk was the highest during the first 2 to 4 weeks of treatment.<sup>23,24</sup> A higher risk of developing infection was also demonstrated in a retrospective study with cancer patients taking morphine as compared to individuals treated with oxycodone, the latter being associated with lower immunosuppressive properties.<sup>136</sup> In another study done in a cancer population, the risk for developing infections did not differ among different opioids (morphine, fentanyl and oxycodone) used but was correlated with increased dose (10 mg elevation of MEDD was associated with the increase in risk of infection by 2%).<sup>137</sup>

Opioid use (predominantly non-medical use) is frequent in HIV-infected patients. Based on experimental studies, it appears that mu opioid agonists may potentiate HIV replication.<sup>135,138,139</sup> In accordance with these investigations a human report performed in 200 subjects divided into four groups depending on HIV + or HIV – status and the use of opioids demonstrated that opioid use was associated with higher viral load and lower CD4+ T cell count.<sup>140</sup>

## Cardiovascular Complications

Opioid peptides and opioid receptors are implicated in modulation of electrophysiological function, heart rate and vascular function and play a role in pathophysiology of cardiovascular (CV) diseases.<sup>141</sup> Secondary to vasodilatation and reduction of cardiac output, opioids may cause hypotension, orthostatic hypotension, pulmonary edema and syncope. Opioids can also produce sinus bradycardia,

supraventricular tachycardia and atrial fibrillation, may impair atrioventricular conduction, and prolong the QT interval, with the risk of *torsades de pointes*. The highest risk of the latter is known to occur with methadone use.<sup>15</sup> All these actions are mediated by activation of peripheral opioid receptors as well as opioid-independent mechanisms (including histamine release mediated by morphine). Importantly, opioids may also affect the efficacy of drugs used in the treatment of CV diseases. For example, morphine was shown to decrease serum concentration of oral P2Y12 inhibitors, such as clopidogrel and ticlopidine.<sup>142</sup> The mechanism of this interaction seems to be related to the delay in gastric emptying and decreased absorption of antiplatelet agents. Opioids may enhance the hypotensive effect of antihypertensive drugs.

A number of observational and experimental studies that have raised concerns regarding the safety of opioids in CV diseases have been published. For example, in a nested case-control study that included over 11,500 patients with myocardial infarction (MI), the current use of opioids was associated with a 28% increased risk for MI compared with non-use.<sup>16</sup> The risk was highest for people treated with morphine and meperidine. Individuals with cancer and major risk factors for MI were excluded from the study. In a cohort study involving almost 150,000 individuals receiving opioids for chronic pain for >180 days and over 120,000 users of cyclooxygenase-2 inhibitors, the risk of MI was determined to be 2.7 and 1.7–1.9 times higher in these two groups of patients, respectively, compared with the general population.<sup>143</sup> Higher doses of opioids were associated with a higher risk. Patients with a history of MI or coronary revascularization and with a diagnosis of cancer were excluded from this analysis.

An interesting observation was done in a cohort study comparing safety of opioids, COX2-inhibitors and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in older individuals (mean age 80) who initiated the use of analgesics. Compared with non-selective NSAIDs, the use of opioids increased the risk of all CV events by 77%, the risk of heart failure increased by 63%, the risk of MI more than doubled and out-of-hospital cardiac deaths were nearly twice the risk induced by NSAIDs.<sup>25</sup> Importantly, the risk of CV events in patients using opioids exceeded the risk in individuals receiving COX-2 inhibitors in this sample. In a retrospective cohort study including approximately 23,000 patients (mean age 48), the use of long-acting opioids was associated with a 65% increase in the risk

of CV death as compared to analgesic anticonvulsants or low doses of cyclic antidepressants.<sup>26</sup>

## Influence on Sleep Quality and Sleep-Disordered Breathing

On the contrary to common beliefs that opioids improve sleep, studies demonstrate, however, that opioid treatment can impair sleep quality and sleep architecture as well as contribute to daytime fatigue and sleepiness. Opioids can curtail total sleep length and sleep cycle length. Patients may wake more often and their stage N2 non-rapid eye movement sleep (light sleep) and transitions to wakefulness can be lengthened, whereas stage N3 (deep sleep) and the rapid eye movement stages can be shortened.<sup>144,145</sup> Because of the suppressive effect on respiratory rate and tidal volume, as well as hypoxic and hypercapnic respiratory drive, opioid use may lead to a spectrum of respiratory derangements during sleep, including hypoventilation, hypoxemia, irregular breathing and apnea. Opioid use may induce sleep-disordered breathing (SDB), mostly of the central type, because of the influence of opioids on breathing rhythm and control of ventilation.<sup>17,18,146–149</sup> Opioids can also trigger or exacerbate obstructive sleep apnea in predisposed individuals by causing relaxation of pharyngeal tone and increasing the collapsibility of the airways.<sup>17,146,147</sup> Studies included in two systematic reviews demonstrated high prevalence of SDB and central sleep apnea (CSA) in patients using opioids for chronic pain, ranging from 75% to 91%, and 18% to 33%, respectively.<sup>18,146</sup> The risk of CSA was demonstrated to be higher in patients with lower body mass, when the dose of oral opioid  $\geq 200$  MEDD and opioids were combined with benzodiazepines or other CNS depressant agents.<sup>17,146,148</sup> Significant sleep disturbances were also demonstrated in an observational investigation in patients with advanced cancer (84%).<sup>147</sup> Sleep apnea may contribute to arrhythmias, myocardial infarction, stroke and increased mortality.<sup>17,26,146,150–152</sup>

## Opioid-Induced Bowel Dysfunction

Opioids affect bowel function through binding to peripheral opioid receptors spread throughout the gastrointestinal (GI) tract. Constipation occur in above 40% of individuals using opioids, and GI pseudo-obstruction may develop as a serious consequence.<sup>5,6,19,20,153,154</sup> In a cohort of elderly patients, the hazard ratio of developing bowel obstruction in individuals prescribed opioids

for chronic pain compared to those who used nonselective NSAIDs exceeded 4.<sup>25</sup> A variant of opioid-induced bowel dysfunction is narcotic bowel syndrome (NBS).<sup>155–159</sup> Patients receiving opioids for the treatment of pain actually become more sensitive to painful stimuli and experience worsened abdominal pain with escalating opioid doses and improvement after cessation of opioids. The underlying pathophysiology of this syndrome is not fully understood. In parallel to other functional GI disorders, it may result from increased segmental motility and opioid-induced hyperalgesia.<sup>20,158,159</sup> The real prevalence of NBS is not known and the syndrome is likely to be unrecognized.<sup>156–158</sup>

A newer but significant concept concerns the influence of a persistent opioid-induced decrease in gastrointestinal motility on the bowel microbiome.<sup>160–165</sup> Opioid-induced changes in the gut microbiome include considerable reduction of the microbiota and a significant increase in pathogenic communities of bacteria, as well as significant impairment of bile acids and morphine (and some other opioids) metabolism in the gut.<sup>160–162,166</sup> Usually, considerable amounts of morphine glucuronides are converted by bowel bacteria back to morphine and reabsorbed to the circulation (enterohepatic circulation).<sup>167</sup> Disturbance of this mechanism may at least partly explain the development of tolerance to opioids, as a considerable amount of the dose of morphine applied is lost with faeces and not reabsorbed.<sup>161</sup> Moreover, changes in the microbiome and intestinal epithelial integrity and function caused by opioids increase the permeability of the gut barrier and promote bacterial translocation to the tissues and release of inflammatory mediators.<sup>97,168</sup> The inflammatory processes induced by opioids may lead to modulation of the anti-nociceptive responses to these drugs.<sup>160,161,163,169</sup> Clinical evidence for both of these mechanisms are still lacking.

## Risk of Unintentional Opioid Overdose and Increased Mortality

Evidence shows that non-medical use of opioids is associated with increased risk of all-cause mortality and overdose death.<sup>170</sup> According to a systematic review, mortality risk in individuals taking opioids for chronic pain relative to populations with similar clinical characteristics not prescribed opioids cannot be definitively estimated at present because of methodological

limitations of published studies.<sup>27</sup> However, a number of individual epidemiological investigations published so far indicated that patients treated with opioids for chronic pain may be susceptible to a higher risk of injuries, poisoning and mortality.<sup>25,26,132,171–180</sup> For example, in a trial concerning approximately 10,000 patients with chronic non-malignant pain treated with opioids, 51 cases of opioid overdose, including 6 (12%) opioid-related deaths, were identified. Patients receiving  $\geq 100$  mg of MEDD had a 1.8% annual overdose rate.<sup>171</sup> Another interesting study showed a 90% increased risk of out-of-hospital deaths associated with the use of both low and high doses of long-acting opioids as compared to antiepileptics and low-dose antidepressants. The risk in less than one-third of the cases was related to opioid overdose, and the most frequent cause of non-overdose deaths were CV events.<sup>26</sup> The risk of increased out-of-hospital mortality was higher in patients using morphine and fentanyl than in those using oxycodone in another cohort study of the same group.<sup>175</sup> Importantly, opioids (including tramadol) were demonstrated to cause higher risk of mortality among patients treated for chronic non-malignant pain than NSAIDs.<sup>25,176</sup> The risk of opioid-related death may be increased with the use of long-acting opioids, at a higher dose range, within 4 weeks after opioid initiation. The concomitant use of gabapentin, benzodiazepines, antidepressants and antipsychotics further increases the risk. Men are more susceptible to these complications, especially those with a history of alcohol abuse, than women. Finally, the prescription of opioids by more than one physician and having them dispensed by more than one pharmacy are predictors of toxicity and the risk of mortality.<sup>26,132,171–174,179,180</sup>

## Discussion

Increasing the access to effective and safe analgesia is a priority in view of unmet needs and common undertreatment of pain around the world.<sup>181,182</sup> Opioids are the most important drugs in the treatment of severe pain.

The present review shows that this therapy may be, however, associated with numerous of potentially serious adverse effects, which may in fact already have occurred early in the treatment. Some complications may develop insidiously and remain undetected or be erroneously attributed to underlying chronic disease or other causes. However, what appears important is that the level of risk may depend on the type of opioid, the dose used, time since opioid initiation, and the formulation. For example, buprenorphine was demonstrated

to pose a lower risk of hypogonadism and immunosuppression compared to other opioids.<sup>52–54,86,91,92</sup> Thus, if these observations are confirmed in future studies, this drug may be chosen whenever it provides adequate analgesia. Opioids differ in the affinities to opioid receptors and some of them possess additional non-opioid mechanism of action, such as, for example, methadone which blocks NMDA receptors or tapentadol that inhibits reuptake of norepinephrine. These differences may underlie the diversities of opioid adverse effects; however, this issue is poorly investigated. The highest risk of some of potential consequences of opioid treatment, such as fracture and mortality, was associated with the use of higher doses of opioids within 2–4 weeks following their implementation. Pain therapy can be optimized by keeping the dose of an opioid as low as possible when using multi-modal treatment with close monitoring, particularly in the period of opioid titration. Further studies focusing on specific opioids used in different dose ranges and types of formulations may guide future strategies in opioid treatment.

Most, if not all, complications of opioid therapy presented in this review have complex pathophysiology, and multiple confounding factors make the results difficult to interpret. Pain itself can, for example, inhibit the immune system and be associated with shorter survival.<sup>28,30,123</sup> Patients with serious life-limiting diseases may already be immunosuppressed, which may be further aggravated by the frequent use of corticosteroids and other immunosuppressive medications.<sup>3,13,183</sup> Using corticosteroids or metoclopramide may also cause hypogonadism.<sup>184,185</sup> Patients may use other CNS depressants associated with an increased risk of fall-related fractures (for example, antipsychotic agents, benzodiazepines and antidepressants).<sup>186–188</sup>

## Study Limitations

The present article was based on a comprehensive literature review. The included studies have different limitations and need to be interpreted cautiously. Many of them were uncontrolled trials and retrospective in nature. Some of them were not designed to assess the adverse effect of opioids as a primary goal. Knowledge of the immunosuppressive and cancer-promoting effects of opioids as well as changes in the bowel microbiome has been derived mostly from animal studies, and studies in humans are so far lacking. The most widely studied drug is morphine, and a smaller percentage of data concerned other opioids, which may differ in their mechanism of action and effects.

Human experimental studies included a small number of patients and multiple additional factors contributed to

their results, so they cannot be considered conclusive as yet. The presence of cancer was an exclusion criterion in cohort epidemiological studies assessing adverse effects such as, for example, the risk of CV events, which is why these data cannot be directly related to patients with cancer, who mostly need long-term opioid therapy. Epidemiological investigations with populations treated with opioids were also related to certain regions and countries of the world and cannot be directly extrapolated to others. Most studies demonstrating high risk of mortality were performed in North America.

## Conclusions

Three important conclusions can be drawn at the moment. First, long-term use of opioids increases the risk of drug-related events and may cause serious adverse effects in a significant number of patients. However, we need many more studies in humans to assess the risk associated with the use of a specific opioid analgesic and its clinical significance. Second, the risk of adverse effects of long-term therapy needs to be taken into consideration when pain is treated with opioids. Health care providers and pharmacists should discuss them with patients, prevent complications, if possible, and ensure timely diagnosis and adequate management. Third, future strategies for the treatment of chronic pain need to develop adequate methods to minimize adverse effects of opioids, including dose reduction, discontinuation and switching to opioid and non-opioid alternative analgesics in order to guide physicians' decisions about treatment and provide patients with optimal care.

## Disclosure

The authors declare no conflicts of interest.

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