REVIEW ARTICLE

Management of cancer pain: challenging the evidence of the recent guidelines for opioid use in palliative care

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ABSTRACT

Opioid therapy is indisputably the mainstay of cancer pain management. However, important issues such as the worldwide variability in the availability and accessibility of opioids, myths and misconceptions about opioid use, and lack of knowledge about prescribing opioids among health care professionals have been pointed out by researchers, clinicians, and several health organizations. In an attempt to improve cancer pain management, guidelines for opioid use were elaborated to assist practitioners in prescribing opioids for the management of cancer-related pain. Recent opioid guidelines were developed based on a systematic assessment of evidence and they are considered one of the best resources to improve knowledge and clinical practice. However, most of the recommendations for cancer pain management included in these guidelines are based on low levels of evidence, which demonstrates that more studies on the use of opioids in pain management are necessary. Moreover, the increased frequency of prescribing opioids for chronic noncancer pain has raised other issues, such as iatrogenic adverse effects, which may also occur in patients with cancer pain on long-term opioid therapy (L-TOT). In this narrative review, we discussed the role of opioid guidelines and recent knowledge regarding the consequences of L-TOT, in particular opioid addiction and deficiencies of the immune and endocrine systems. Finally, we addressed new strategies to strengthen the L-TOT in the management of cancer-related pain among patients in palliative care.

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Introduction Opioids are highly recommended by the World Health Organization (WHO),[1] particularly in cancer pain management,[2] due to their advantageous analgesic effect, multiple routes of administration, ease of titration, and lack of dose-ceiling effect. Thus, opioid therapy is still the mainstay of pain relief and quality of life improvement in patients with cancer-related pain.[3] Its potent effects, especially in patients with advanced cancer pain, has encouraged clinicians to prescribe opioids to patients with chronic noncancer pain of difficult management. In the early 1990s, the current opioid epidemic in the United States (US) was founded on a movement aimed to address the problem of undertreated chronic noncancer pain. Thus, the success of opioid treatment in patients with advanced cancer set the stage for extending the same treatment principles to the management of chronic pain of various etiology.[4] A radical shift occurred in treatment approaches for chronic noncancer pain, including a campaign by professional pain societies and the US Joint Commission to consider pain the "fifth vital sign." In 1997, the American Pain Society and the American Academy of Pain Medicine published a consensus statement recommending the use of opioids to treat chronic noncancer pain, arguing that the risk of opioid addiction was minimal. Contemporarily, a broad array of pharmaceutical industries concerted efforts to promote opioids as a safe, nonaddictive, effective, and humane alternative to treat chronic noncancer pain. These marketing efforts certainly accelerated the shift in the treatment paradigm

for chronic noncancer pain.[5] Today, in some high-income countries, the high consumption of opioids for chronic noncancer pain, despite the continuing weak evidence regarding the benefits of long-term opioid therapy (L-TOT),[6] has therefore resulted in increased reporting of iatrogenic opioid effects which, besides the classic adverse effects, comprise addiction and emerging evidence for suppression of the immune and endocrine systems.[7-10]

Consequently, the knowledge derived from iatrogenic opioid effects in chronic noncancer pain individuals has raised concerns that they can also occur in patients with cancer pain on L-TOT.[11] Nowadays, patients with cancer have longer life expectancy and higher survival rates thanks to advances in the diagnostic methods and treatments, which may also prolong the opioid treatment for cancer-related pain. Therefore, with widespread opioid use and improvement of anticancer therapies, there is a growing interest in the effects of L-TOT in cancer patients. Simultaneously, the palliative care needs of patients in early stages of cancer trajectories have been progressively recognized and addressed, including the need for adequate pain management.[12]

It should be underpinned that the distorted patterns of the worldwide availability and accessibility of opioids are a sensitive and complex issue. There are high-income countries in opioid crisis fighting against the iatrogenic opioid overuse and there is a global pain crisis involving many middle- and low-income countries with limited access to opioids. A balanced approach including, among others, regulations on prescribing opioids and adequate training of health care professionals is recommended to improve the access to pain treatment with opioids.[13] In this context, all information derived from studies of L-TOT can contribute to expanding our knowledge and understanding of the benefits and risks of opioid use in different clinical scenarios and to developing recommendations to guide the clinical practice.

Therefore, the primary goal of this review was to provide and discuss new knowledge regarding the emerging consequences of L-TOT in patients with cancer. Particularly, opioid addiction and new evidence of deficiencies of the immune and endocrine systems as a consequence of L-TOT may represent future challenges.

The role of guidelines An important response to the phenomenon of opioid overprescription in high-income countries has been the elaboration of opioid guidelines intended to decrease the risk of deleterious effects associated with the use and diversion of prescribed opioids. Many national and international opioid guidelines have been published and, according to a review comparing 7 published guidelines for L-TOT for chronic noncancer pain, they were similar in their recommendations and seemed to show broad consensus in many areas.[14] The most influential set of opioid guidelines within the US has been the 2016 Centers for Disease Control and Prevention guideline for prescribing L-TOT for adults with chronic noncancer pain.[15] These guidelines were explicitly formulated as a response to the opioid overdose epidemic and were intended to address both the public health crisis of opioid overdose and chronic pain. The guidelines were further intended to enhance communication about the benefits and risks of opioid therapy and treatment effectiveness, and to reduce the risks of L-TOT, including opioid addiction. They were developed through a systematic review of evidence, that is, the evidence for each recommendation was weighed and rated based on the level of evidence and strength of recommendation. The principles were straightforward: opioids should be prescribed only when necessary and at the lowest effective dose, the patient should be regularly assessed for potential harms, and the drug should be tapered or stopped if used inappropriately. Furthermore, the guidelines stressed the importance of communication with the patient and the family.

Since its development in 1986, the WHO 3-step analgesic ladder has been a worldwide guideline for professionals treating cancer-related pain. The analgesic ladder is the central approach of the 1996 WHO guidelines on cancer pain relief, in which the choice of an analgesic is determined by the intensity of pain.[16] In step I, nonopioids (paracetamol or nonsteroidal anti-inflammatory drugs) are proposed for the management of mild pain; in step II, the so-called weak opioids (eg, codeine or tramadol) are proposed to be prescribed in cases of mild-to-moderate pain; and in step III, the so-called strong opioids are proposed for the management of moderate-to-severe pain. Despite the widespread use of this ladder principle, unrelieved pain continues to be a substantial concern in one-third of patients with either solid or hematologic malignancies. However, the most recent guidelines based on systematic, evidence-based grading, including the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the WHO guidelines,[1,3,17] demonstrate that most of the recommendations for cancer pain management are based on low levels of evidence, and it seems obvious that there is an urgent need for further research that should be conducted to upgrade the quality of evidence and the grades of recommendations. Of interest, for the management of mild-to-moderate cancer-related pain, the latest ESMO guideline recommended the use of the drugs listed in step II of the WHO analgesic ladder (level of evidence, III; grade of recommendation, C), but it also acknowledged the use of low doses of step III opioids as an alternative to step II opioids,[18] (level of evidence, II; grade of recommendation, C).[3] Likewise, the latest NCCN guideline recognized the use of step III opioids for moderate cancer pain, with an NCCN category and consensus of 2A (ie, based upon lower-level evidence, but for which there is an NCCN consensus that the intervention is appropriate).[17]

Apart from the NCCN guideline which includes a short section on preventing opioid misuse and abuse, the recent guidelines provide very limited information beyond the traditional adverse effects about the risks of L-TOT in patients with cancer. This lack of information is associated with the currently limited scientific evidence, which we will seek to discuss in the following sections.

Opioid addiction In the past few years, the terms *chemical coping*, *nonmedical opioid use*, *opioid misuse*, *opioid addiction*, *aberrant opioid behavior*, among others, have been used in cancer-related pain research to denominate drug-seeking behavior, which occurs when patients use opioids in a nonprescribed way to cope with various stressful conditions and symptoms.[19-21] In general, addiction is considered when the use of opioids crosses the line between normal nonaddictive opioid use for pain to pure addiction, which involves compulsive and destructive behavior.[22] It is possible that many patients may perceive emotional pain as physical pain and an attempt to treat both types of pain with opioids may lead to medication misuse. Unfortunately, emotional distress is integrated into the central pain pathways in a way which accentuates physical pain processing, so these distinctions are usually very challenging.[23] Moreover, besides a subjective sensation of urge or craving for using opioids, physiological features of dependence (physical dependence) may be present, such as tolerance to the effects of opioids, withdrawal symptoms following cessation or dose reduction, or repeated use of opioids or similar pharmacological substances to prevent or alleviate withdrawal symptoms.[24] Finally, the growing confidence within palliative care to treat complex and multiple concomitant symptoms with opioids may increase the frequency of their prescription and, consequently, the risk for iatrogenic addiction.

Indeed, opioid addiction can create significant problems for patients, who are already affected by a serious and life-threatening disease (cancer). Besides the classic complications including neuro-toxicities, respiratory depression, and death,[24] consequences of opioid addiction may not be recognized timely as patients with cancer often have problems with compliance and, therefore, may not be able to carry out anticancer treatments and comply with medication regimes, which is often the prerequisite for successful pain management. Thus, these patients will possibly have both a pain and an addiction problem on top of their life-threatening disease, which may interact negatively with each other and may require the use of several treatment strategies. Moreover, deleterious societal and economic impact of opioid addiction may be observed in family / social relationships, job performance, and increased costs for the health care and even the criminal justice systems.[25]

Previous studies have indicated that the prevalence of opioid addiction varies up to 7.7% in cancer-related pain, depending on the subpopulations studied and the criteria used.[26] However, a recent North American study analyzed the frequency and factors predicting the risk for aberrant drug-related behavior among 729 opioid-treated patients with cancer who received an outpatient supportive care consultation at a comprehensive cancer center; out of them, 20% were at risk of aberrant opioid use and 11%, of drug and alcohol use.[27] Although opioids are the gold-standard analgesics in cancer pain management, emerging evidence suggests that patients with cancer might be at a higher risk of addiction than previously thought.[12,20,21] Therefore, the following recommendations for screening, monitoring, and treatment programs have been recently proposed with regard to opioid therapy for patients with cancer:[20,21]

- Patient assessment (eg, psychosocial or genetic dispositions);
- Pain syndrome assessment (eg, considering alternative drugs in the case of neuropathic pain);
- Screening of all patients with validated risk assessment tools;
- Education and goal-setting for health care professionals as well as the patients and their families;
- Selection of opioids (eg, type of drug, dose, and exposure time);
- Monitoring (eg, drug prescription databases, behaviors, and urine drug tests);
- Exit programs (tapering off) and evidence-based treatment of addiction.

These recommendations have been fostered in the US in light of the ongoing opioid epidemic and inspired by the guidelines already developed for opioid therapy of patients with chronic noncancer pain; however, it seems likely that the changing trajectories and environment for cancer care in high-income countries aligned with the high opioid consumption in general may pave the way for similar recommendations in the upcoming European guidelines for cancer pain management.

Opioids and the immune system There are hypotheses that opioid use is associated with increased risk of infections[28] and the development / progression of cancer,[29] which may be due to the suppression of the immune system. The immune system has a fundamental role in controlling and eliminating cancer cells and preventing them from growing. Moreover, patients with cancer have a higher risk of infection. Therefore, preservation and promotion of a competent immune system in this group is crucial, as is the role of opioids in providing pain relief.

In vitro animal and human studies regarding acute pain indicated that opioids may modulate the immune system through numerous mechanisms and that the way the immune system is modulated varies for different opioids.[30-34] Opioid use may induce direct effects on the composition and function of lymphocytes and natural killer (NK) cells,[35,36] it may also cause a reduction in

the absolute numbers of different cell types,[30,32] generation of an immune signal leading to a neuroinflammatory reaction reducing the opioid analgesic effect,[37] suppression of NK cell activity,[38] and cytokine production.[39] A few smaller studies in patients with chronic noncancer pain on L-TOT also suggested associations with lower proportions of NK cells and CD56bright NK cells, a higher proportion of interleukin (IL) 2–activated NK cells, and a higher concentration of IL-1β.[10]

The paucity of studies regarding the effects of opioids on the immune system of patients with cancer has been demonstrated in a systematic review which identified 5 observational studies investigating the effect of morphine alone on immunologic markers.[40] The results indicated weak evidence regarding a potential impact of morphine on the immune system that could be dependent on the length of treatment, route of administration, and the immune parameters examined. An increase in the synthesis and secretion of IL-2 by lymphocytes after 4 weeks of morphine treatment, increased NK and lymphokine-activated killer cell activity, and a higher proportion of $CD3^+$ and $CD4^+$ T cells in the peripheral blood mononuclear cell preparations were observed.[40] Finally, divergence among the studies makes the comparison difficult, especially regarding different types of opioids, administration routes, and immune parameters investigated. For future studies, we recommend increasing sample sizes based on power calculations, conducting randomized controlled trials with control groups consisting of patients with cancer, and performing baseline examination of measures of the innate and the adaptive immune systems followed by regular follow-ups to detect possible time-dependent alterations. In light of the above, it seems obvious that there is an urgent need for research on the effects of opioids on the immune system. Such research should be funded and designed to upgrade the level of evidence and the grades of recommendations.

Opioids and the endocrine system Assumptions that opioids can interfere with the endocrine system have focused the attention not only on sexual dysfunctions, but also the effects of opioids on other hormones, which may lead to harmful long-term effects and cause diverse endocrine disorders, such as hyperprolactinemia and hyperthyroidism. Furthermore, symptoms of hypogonadism include fatigue and depression, which are commonly found in people with advanced cancer.

Hormonal dysfunction related to opioid use has been demonstrated in a few studies conducted in animals and humans.[35,41] Studies in animals have shown acute and chronic effects of opioids on the endocrine system, mediated both centrally (via the hypothalamic pathway) and peripherally (via a direct effect on the gonads).[41] Clinical studies have demonstrated primary and secondary opioid-induced hypogonadism in patients with noncancer pain receiving opioid treatment.[42-44] Moreover, the effect may be dose-dependent[44] and each opioid may have different endocrine effects.[45-47] In patients with cancer-related pain, signs and symptoms of central hypogonadism and sexual dysfunction related to L-TOT have been observed.[48,49]

A systematic review regarding the effect of opioids on the hypogonadal axis of cancer patients included 4 studies. Of them, 3 indicated a dose-dependent relationship between opioid use and hypogonadism. The results included relationships between opioid use and reduced luteinizing hormone (LH), follicular stimulating hormone (FSH), and testosterone levels in men and reduced LH ($P = 0.033$) and FSH ($P = 0.03$) levels in postmenopausal women. Evidence of symptomatic hypogonadism and reduced survival have also been indicated.[50] A current recommendation is to screen patients with cancer for sex hormone deficiency before and during L-TOT and to consider risks and benefits of testosterone supplement therapy. Finally, further research is urgently needed to upgrade the level of evidence and the strength of recommendations.

Conclusions The implementation and dissemination of evidence-based information on the use of L-TOT in cancer pain management, especially in the context of early palliative care interventions, may be a powerful resource to avoid opioid addiction. Moreover, further dissemination of scientific information may encourage new research initiatives leading to a robust knowledge on cancer pain management. Well-designed studies on the management of pain in cancer and noncancer patients can contribute to generating new insights on some of the novel aspects, such as the effect of opioid on the immune and endocrine systems, which can hopefully soon reach acceptable levels of evidence so as to be included as recommendations in future guidelines.

First, the publication of guidelines based on systematic reviews is a major step forward and it is mandatory that these guidelines be continuously updated. However, since opioids are an old class of drugs, it is in fact remarkable that a substantial part of opioid management that takes place in everyday clinical practice is not based on solid evidence. On the contrary, the evidence is often weak. Second, according to recent randomized controlled trials in complex palliative interventions, it is quite disappointing to note that pain management of patients with advanced cancer seems not to be very successful. The major outcomes of these studies demonstrate an improved general quality of life, but seldom an adequate symptom control, including substantial pain relief. Therefore, it is mandatory that the evidence-based pain management and opioid guidelines based on international consensus be implemented and adapted to local needs. Upcoming studies from around the world focusing on cancer pain management programs have actually demonstrated that meticulous monitoring and management strategies in relevant local environments based on

intensive teaching and mentorship can improve the skills of the health care staff and produce excellent outcomes.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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REFERENCES

1 World Health Organization (WHO). WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. 2018. https://www.who.int/publications/i/item/9789241550390

2 Ventafridda V, Tamburini M, Caraceni A, et al. A validation study of the WHO method for cancer pain relief. Cancer. 1987; 59: 850-856.

3 Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann. Oncol. 2018; 29: iv166-iv191.

4 Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. BMJ. 2016; 352: i20.

5 Cerdá M, Krawczyk N, Hamilton L, et al. A critical review of the social and behavioral contributions to the overdose epidemic. Annu Rev Public Health. 2021; 42: 95-114.

6 Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010; 2010 (1): CD006605.

7 Højsted J, Nielsen PR, Guldstrand SK, et al. Classification and identification of opioid addiction in chronic pain patients. Eur J Pain. 2010; 14: 1014-1020.

8 Højsted J, Kurita GP, Kendall S, et al. Non-analgesic effects of opioids: the cognitive effects of opioids in chronic pain of malignant and non-malignant origin. An update. Curr Pharm Des. 2012; 18: 6116-6122.

9 Gudin JA, Laitman A, Nalamachu S. Opioid related endocrinopathy. Pain Med. 2015; 16: S9-S15.

10 Diasso PDK, Birke H, Nielsen SD, et al. The effects of long-term opioid treatment on the immune system in chronic non-cancer pain patients: a systematic review. Eur J Pain. 2020; 24: 481-496.

11 Fredheim OM, Skurtveit S, Sjøgren P, et al. Prescriptions of analgesics during chronic cancer disease trajectories: a complete national cohort study. Pharmacoepidemiol Drug Saf. 2021; 30: 1504-1513.

12 Gaertner J, Boehlke C, Simone CB 2nd, Hui D. Early palliative care and the opioid crisis: ten pragmatic steps towards a more rational use of opioids. Ann Palliat Med. 2019; 8: 490-497.

13 Bhadelia A, De Lima L, Arreola-Ornelas H, et al. Solving the global crisis in access to pain relief: lessons from country actions. Am J Public Health. 2019; 109: 58-60.

14 Cheung CW, Qiu Q, Choi SW, et al. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. Pain Physician. 2014; 17: 401-414.

15 Dowell D, Haegerich T, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. JAMA. 2016; 315: 1624-1645.

16 World Health Organization. Cancer Pain Relief. 2nd ed. Geneva, Switzerland: World Health Organization; 1996.

17 Swarm RA, Paice JA, Anghelescu DL, et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019; 17: 977-1007.

18 Bandieri E, Romero M, Ripamonti CI, et al. Randomized trial of low-dose morphine versus weak opioids in moderate cancer pain. J Clin Oncol. 2016; 34: 436-442.

19 Kwon JH, Tanco K, Park JC, et al. Frequency, predictors, and medical record documentation of chemical coping among advanced cancer patients. Oncologist. 2015; 20: 692-697.

20 Arthur J, Bruera E. Balancing opioid analgesia with the risk of non-medical opioid use in patients with cancer. Nat Rev Clin Oncol. 2019; 16: 213-226.

21 Dalal S, Bruera E. Pain management for patients with advanced cancer in the opioid epidemic era. Am Soc Clin Oncol Educ Book. 2019; 39: 24-35.

22 Del Fabbro E. Assessment and management of chemical coping in patients with cancer. J Clin Oncol. 2014; 32: 1734-1738.

23 Berna C, Vincent K, Moore J, et al. Presence of mental imagery associated with chronic pelvic pain: a pilot study. Pain Med. 2011; 12: 1086-1093.

24 Smith SM, Dart RC, Katz NP, et al; Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain. 2013; 154: 2287-2296.

25 Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. Mayo Clin Proc. 2009; 84: 593-601.

26 Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. Eur J Pain. 2007; 11: 490-518.

27 Yennurajalingam S, Edwards T, Arthur JA, et al. Predicting the risk for aberrant opioid use behavior in patients receiving outpatient supportive care consultation at a comprehensive cancer center. Cancer. 2018; 124: 3942-3949.

28 Al-Hashimi M, Scott SW, Thompson JP, Lambert DG. Opioids and immune modulation: more questions than answers. Br J Anaesth. 2013; 111: 80-88.

29 Sjøgren P, Kaasa S. The role of opioids in cancer progression: emerging experimental and clinical implications. Ann Oncol. 2016; 27: 1978-1980.

30 Dutta R, Krishnan A, Meng J, et al. Morphine modulation of toll-like receptors in microglial cells potentiates neuropathogenesis in a HIV-1 model of coinfection with pneumococcal pneumoniae. J Neurosci. 2012; 32: 9917-9930.

31 Cornwell WD, Lewis MG, Fan X, et al. Effect of chronic morphine administration on circulating T cell population dynamics in rhesus macaques. J Neuroimmunol. 2013; 265: 43-50.

32 Meng J, Yu H, Ma J, et al. Morphine induces bacterial translocation in mice by compromising intestinal barrier function in a TLR-dependent manner. PLoS One. 2013; 8: e54040.

33 Velásquez JF, Ramírez MF, Ai DI, et al. Impaired immune function in patients undergoing surgery for bone cancer. Anticancer Res. 2015; 35: 5461-5466.

34 Franchi S, Moschetti G, Amodeo G, Sacerdote P. Do all opioid drugs share the same immunomodulatory properties? A review from animal and human studies. Front Immunol. 2019; 10: 2914.

35 Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain. 2009; 25: 170-175.

36 Suzuki S, Miyagi T, Chuang TK, et al. Morphine upregulates mu opioid receptors of human and monkey lymphocytes. Biochem Biophys Res Commun. 2000; 279: 621-628.

37 Hutchinson MR, Bland ST, Johnson KW, et al. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. ScientificWorldJournal. 2007; 7: 98-111.

38 Bayer BM, Daussin S, Hernandez M, Irvin L. Morphine inhibition of lymphocyte activity is mediated by an opioid dependent mechanism. Neuropharmacology. 1990; 29: 369-374.

39 Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. Am J Ther. 2004; 11: 354-365.

40 Boland JW, McWilliams K, Ahmedzai SH, Pockley AG. Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review. Br J Cancer. 2014; 111: 866-873.

41 Vuong C, Van Uum SH, O'Dell LE, et al. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocr Rev. 2010; 31: 98-132.

42 Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002; 3: 377-384.

43 Roberts LJ, Finch PM, Pullan PT, et al. Sex hormone suppression by intrathecal opioids: a prospective study. Clin J Pain. 2002; 18: 144-148.

44 Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain. 2008; 9: 28-36.

45 Cicero TJ, Bell RD, Wiest WG, et al. Function of the male sex organs in heroin and methadone users. N Engl J Med. 1975; 292: 882-887.

46 Bliesener N, Albrecht S, Schwager A, et al. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab. 2005; 90: 203-206.

47 Hallinan R, Byrne A, Agho K, et al. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. Int J Androl. 2009; 32: 131-139.

48 Garcia JM, Li H, Mann D, Epner D, et al. Hypogonadism in male patients with cancer. Cancer. 2006; 106: 2583-2591.

49 Strasser F, Palmer JL, Schover LR, Yusuf SW, et al. The impact of hypogonadism and autonomic dysfunction on fatigue, emotional function, and sexual desire in male patients with advanced cancer: a pilot study. Cancer. 2006; 107: 2949-2957.

50 McWilliams K, Simmons C, Laird BJ, Fallon MT. A systematic review of opioid effects on the hypogonadal axis of cancer patients. Support Care Cancer. 2014; 22: 1699-1704.