Recommendations for the use of opioids in Brazil: Part IV. Adverse opioid effects*

Recomendações para uso de opioides no Brasil: Parte IV. Efeitos adversos de opioides

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ABSTRACT

BACKGROUND AND OBJECTIVES: Adequate opioid use in the short and long term, as well as diagnosis, management of adverse effects, abuse and chemical dependence of such agents are still an investigation area for many researchers. This study aimed at discussing actions for monitoring, diagnosing and managing adverse effects common to those drugs.
CONTENTS: This article addresses diagnosis and management of common opioid adverse effects, as well as abuse and chemical dependence, discussing the frequency of such alterations, the pharmacological and complementary management, risks associated to therapy and most relevant recommendations.
CONCLUSION: Several are the effects of acute or chronic opioid administration. A recommended strategy is to monitor, diagnose the occurrence and adequately treat effects so that there is no damage for patients needing such substances, thus preventing therapy interruption.
Keywords: Adverse effects, Opioids.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O emprego adequado de opioides em curto e em longo prazo, assim como o diagnóstico, o tratamento dos efeitos adversos, o abuso e a dependência química desses agentes continuam sendo um campo de investigação de vários pesquisadores. O objetivo deste estudo foi discutir as ações para a monitoração, diagnóstico e tratamento dos efeitos adversos comuns a esses fármacos.
CONTEÚDO: Neste artigo abordou-se o diagnóstico e tratamento dos efeitos adversos comuns dos opioides, assim como abuso e dependência química, discutindo a frequência dessas alterações, o tratamento farmacológico e complementar, os riscos associados à terapêutica e as recomendações mais importantes.
CONCLUSÃO: São variados os efeitos adversos decorrentes da administração aguda ou crônica de opioides. Uma estratégia recomendada é monitorar, diagnosticar a ocorrência e tratar os efeitos de forma adequada para que não haja prejuízo para o paciente que necessita dessas substâncias, evitando a interrupção da terapêutica.
Descritores: Efeitos adversos, Opioides.

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INTRODUCTION

The correct and monitored use of opioids is still a challenge for health professionals. So, by initiative of a group of specialists, with institutional validation of the **Brazilian Society for the Study of Pain** (SBED), we decided for a publication, the major proposal of which is to present recommendations to guide health professionals in the use of opioids to control acute and chronic pain. Continuing with our work, this study will discuss the diagnosis and management of opioids adverse effects in the short and long term, also emphasizing abuse and addiction. With this, we close this work, encouraging clinical and experimental research about the applicability of such agents in the daily practice.

CONTENTS

Approximately 90% of patients with chronic pain receive opioids[1], including those with indication of pain management through interventionist techniques[2].
Notwithstanding, the use of opioids is limited by adverse effects such as constipation, nausea, vomiting, respiratory depression and sedation among others less common effects. This helps the withdrawing of such agents, as well as inadequate dose decrease and lack of satisfactory analgesia. In addition to such effects, it is important to remind that opioids induce tolerance and hyperalgesia, abuse and physical dependence, immunomodulatory effects, hormonal changes, sleep disorders and psychomotor disorders[3].

Constipation

This is a common problem with incidence between 40% and 90% of patients treated with opioids and may appear after a single dose. The consequence of constipation along time is related to increased morbidity and mortality and worsening of patients' quality of life. Chronic constipation results in effort to evacuate, formation of hemorrhoids, rectal region pain and burning sensa-

tion, intestinal obstruction with risk of rupture and death[4]. Decreased intestinal mobility results from the activation of *mu* receptors in the gastrointestinal tract, acting directly on the enteric nervous system or decreasing parasympathetic autonomic flow[5]. However, tolerance seen for nausea, sedation and respiratory depression does not occur for opioid-induced constipation. So, there is no improvement of symptoms during the use of opioids and constipation should be adequately monitored and managed. Roma III criteria may be used to define intestinal constipation and are based on: effort to evacuate, hardened or fragmented stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockade, manual maneuvers to help evacuation and less than three evacuations per week (Table 1).

The presence of two or more of such criteria in the last six months characterizes intestinal constipation, being that each criterion may be considered positive when reaching the following cutoff points: 1) evacuation effort in at least 25% of defecations – answer equivalent to "frequently" (question A≥2); 2) hardened or fragmented stools in at least 25% of defecations – answer equivalent to "frequently" (question B≥2); 3) sensation of incomplete evacuation in at least 25% of defecations – answer equivalent to "sometimes" (question D≥1); 5) manual maneuvers to help at least 25% of defecations – answer equivalent to "sometimes" (question E≥1); and 6) less than three evacuations per week[6].

With regard to constipation, it is necessary to reeducate life habits (alcoholism, smoking and practice of physical activities) and dietary habits (fluid and fiber ingestion) which influence intestinal mobility pattern. The recommendation is to consume 14g of fibers for each 1000kcal ingested and adequate ingestion values for fluids for sedentary people is 3.7L/day for males and 2.7L/day for females, being these values higher for physically active people[7]. After optimizing such factors, laxatives may be associated in doses recommended by the literature, respecting contraindications (Table 2).

Effective constipation management requires de use of opioid antagonists, with peripheral action on *mu* receptors, such as methylnaltrexone and alvimopan. These agents act on the gastrointestinal tract sparing central opioid analgesic effect[8]. Recommendations of this article are described in tables 3 and 4[8-15].

Urinary retention

Opioids may decrease tone and contraction strength of the detrusor muscle of the bladder, the sensation of plenitude and the desire to urinate, in addition to decreasing voiding reflex. This effect is more common during acute pain with prevalence from 4% to 18%. Important: 1) investigate other causes for urinary flow decrease, such as renal failure, ureteral obstruction or hypovolemia; 2) avoid anticholinergic drugs; 3) decrease opioid dose; 4) perform bladder voiding maneuvers or bladder catheterization if necessary. Urinary retention may be caused by central or peripheral action on *mu* receptors and may be partially reverted by antagonists[16].

Cardiovascular effect

Cardiovascular effects are not very common. Morphine releases histamine, causing vasodilation and hypotension, which are partially reversed by antagonist H1 or totally reversed by naloxone. Parasympathetic stimulation may also contribute to bradycardia[17]. Prolonged QT interval and *torsade des pointes* (Tdp) syndromes have been recently described, with ventricular tachycardia and cardiac arrest in patients under chronic methadone[18]. Mortality may reach 17% and previous electrocardiographic monitoring is recommended before the use of such agents. In heroin-addicts being treated with methadone, the occurrence of tachycardia related to prolonged QT interval (above 500ms) was 16% and of Tdp rhythm of 3.6%[19].

Some authors have observed that interval above 30ms should be considered significant and above 60ms a risk factor for Tdp

Table 1. Tool to define intestinal constipation based on ROMA III consensus[6]

Criteria	Questions	Options of answers
Evacuation effort	(A) Since six month ago, with which frequency did you have to push to poop?	(0) Never or seldom (1) Sometimes (2) Frequently (3) Most of the times (4) Always
Hardened or fragmented stools	(B) Since six months ago, with which frequency did you have hard, hardened or similar to balls stools?	(0) Never or seldom (1) Sometimes (2) Frequently (3) Most of the times (4) Always
Sensation of incomplete evacuation	(C) Since six month ago, with which frequency you had the sensation of incomplete evacuation, that is, even after pooping you remained willing?	(0) Never or seldom (1) Sometimes (2) Frequently (3) Most of the times (4) Always
Sensation of anorectal obstruction or blockade	(D) Since six month ago, with which frequency you felt that stools could not go through or that were trapped in the anus?	(0) Never or seldom (1) Sometimes (2) Frequently (3) Most of the times (4) Always

Table 2. Major laxatives to treat intestinal constipation[3]

Agents	Formulas	Doses	Adverse effects common to the group
Increases fecal matter			Intestinal obstruction Intestinal gases
Methylcellulose	Powder: 2g Tablet: 500mg	6g/day	
Calcium polycarbophil	Tablet: 625mg	2 tablets 1 to 4 times a day	
Psyllium	Sachet: 5,8g	Dilute in 240 mL of water, 1 to 3 times a day	
Emolients			Contraindicated in association with mineral oil
Docusate calcium	Capsules: 240mg	Once a day	
Docusate sodium	Capsules: 50 to 100mg Liquid: 150mg in 15 mL Syrup: 60mg in 15 mL	50 to 300mg/day	
Osmotic laxatives			Flatulence, abdominal colic, diarrhea, nausea and vomiting
Lactulose	Liquid: 10g in 15 mL	15 to 60 mL/day	Care with diabetics
Magnesium cytrate	Liquid: 296 mL per bottle	500mL to 1 L/day	Attention to chronic renal. Risk of hypermagnesemia
Magnesium hydroxide	Liquid: 400mg per 5 mL	30 to 60 mL once a day	Attention to chronic renal. Risk of hypermagnesemia
Polyethylene glycol 3350	Powder: 17g	Dilute in 240mL water, once a day	
Sodium biphosphate	Liquid: 45 to 90mL	20 to 45mL/day	Attention to renal patients or those with restricted sodium diet
Sorbitol	Liquid: 480mL	30 to 150mL/day	
Stimulants			Stomach ache, abdominal colic, weakness, sweating, rectal irritation, diarrhea, dizziness
Bisacodyl	Tablet: 5mg	5 to 15mg/day	
Cascara	Liquid: 120 mL Tablet: 325mg	5 mL/day or 1 tablet /day	Interaction with digitalis. Prolonged use related to colon adenoma
Castor oil	Liquid: 60mL	15 to 60mL once a day	Contraindicated during pregnancy or lactation
Sena	Tablet: 10.73mg	2 to 3 tablets once or twice a day Not exceed 30mg/day	Fingers edema, colonic melanosis

Table 3. Recommendations to treat constipation based on clinical trials

Education and guidance to patient and relatives are essential to treat constipation.
Transdermal fentanyl is associated to lower incidence of constipation as compared to remaining opioids.
Monotpherapy is less effective than combination of strategies
Polyethylene glycol, sena and lactulose are effective to decrease opioid-induced constipation
Laxative is the preferred strategy by patients.

Table 4. Recommendations to treat constipation based on case reports and opinion of specialists

Fecal matter forming laxatives, osmotic, emollient/lubricants and stimulants are options to control constipation
Evaluate patients' intestinal habits before introducing the opioid helps preventing this adverse event
Abdominal massage, digital rectal examination, suppositories and rectal lubricants are non-pharmacological strategies with good effect to decrease constipation.
Diet rich in fibers associated to increased fluid ingestion, with pre and probiotics, regularization of meals and fluid ingestion are important to control constipation.
A routine of physical activities and exercises may contribute to manage constipation.
Physical measures for prevention and treatment of constipation, such as transcutaneous electric nerve stimulation and acupuncture are effective.
Cognitive and behavioral measures include biofeedback, communication and cognitive therapy and contribute to the management of constipation.
Use gastrocolic reflex as strategy favors adequate frequency of intestinal function.
The use of oral naloxone is limited due to its absorption, breakdown of the blood-brain barrier and reduction of analgesia.

rhythm. This, however, is more common in individuals using methadone doses above 40mg or in concomitant use of CPY3A4 enzyme inhibitors, such as fluoxetine, sodium valproate, clarithromycin and fulconazole. Other drugs, such as tricyclic antidepressants, neuroleptics and erythromycin have been also described as agents which may prolong QT interval. So, it is important to monitor patients using CPY3A4 enzyme inhibitors, those with low potassium levels or altered liver function[20]. So, we conclude that:

1) The possibility of elongating the QT space (including the polymorphic type) and the evolution to ventricular arrhythmia should be considered when using opioids, especially methadone;
2) The use of concomitant drugs which prolong QT interval or which share common metabolism pathways with methadone should be avoided.

Effects on the immune system

Opioids have been implied in the increased incidence of infection in heroin-addict patients and as a facilitator for the pathogenesis of the acquired immunodeficiency virus. Chronic opioid administration may inhibit cell immune response, the production of antibodies, natural killer (NK) cell activity and the expression of pro-inflammatory cytokines[21]. These effects may be related to the action on MOR receptors and to the inhibition of macrophages phagocytic activity and to the action on KOR receptors. The action on KOR receptors, however, increases NK cells activity and humoral immune response[22].

Although several studies point to opioids immunosuppressive effect, the clinical relevance of such observations is still uncertain and works just as a pre-requisite for new investigations in this area. Final recommendations for the use of opioids, in the most different clinical practice situations, with regard to immune consequences of such drugs still cannot be made. Since each substance seems to have a different effect, additional studies with different opioids, in addition to morphine, should be carried out. Still, specific subpopulations, such as immunosuppressed and patients in critical stage, should also be object of research.

Opioid-induced tolerance and hyperalgesia

Most of the times, increasing opioid dose is related to disease progression or tolerance. Tolerance implies the need for increasingly higher doses to obtain the same effect. That is, there is decrease in effectiveness along time. There are two types of tolerance: the innate, which depends on genetic inheritance and the acquired (pharmacokinetic, pharmacodynamic and learned). Pharmacokinetic tolerance is related to changes in drug metabolism after repeated administrations, leading, then, to enzyme induction. However, pharmacodynamic tolerance may be associated to increased opioid receptors. On the other hand, the learned tolerance is related to concepts. Patients take more drugs because they believe they are not effective or that taking more they will feel better. Opioid tolerance is not crossed, and this concept is the basis for the rotation of such agents[23]. Attention is to be paid to opioid-induced toxicity, clinical presentation characterized by sensitivity changes (allodynia and hyperalgesia), by the need for increasingly higher opioid doses, myoclonus, seizure and cardiac arrest[24].

In opioid-induced hyperalgesia, there is a down-deviation of the dose/effect curve, that is, the analgesic effect decreases along time with a certain opioid dose and there is no improvement with dose increase – on the contrary, there may be worsening of pain. Pain is more severe than the original or initial pain, it is poorly defined in terms of quality and location, with decreased tolerability threshold[25]. Recommendations to decrease hyperalgesia are: 1) dose adjustment or opioids rotation; 2) switch to methadone when there is suspicion of hyperalgesia caused by a different opioid; 3) switching to methadone does not eliminate the possibility of hyperalgesia[26]. There are no well-controlled studies assuring the use of dextromethorphan, memantine, propofol, naloxone and ketamine to treat opioid-induced hyperalgesia.

Hormonal alterations

Opioids may induce endocrinopathy. There is report of reduction of total and free testosterone, estrogen, LH, GnRH, DHEA, DHEAS, ACTH, CRH and cortisol[27]. Most studies, however, are focused on androgenic hormones. It has been reported erectile dysfunction, libido reduction, depression, anemia and fatigue. There is free and total testosterone reduction between 1 and 4h after intravenous opioid administration, returning to normal values 24h after drug withdrawal. In chronic pain patients under opioids, smoking predisposes to this alteration. It also seems that this action is different for different opioids, being lower for buprenorphine as compared to methadone. Eighty seven percent of patients using methadone in doses above 100mg per day have major erectile dysfunction and all (100%) have decreased testosterone levels. Transdermal testosterone, however, may decrease several alterations induced by chronic opioid use[28]. In females, there may be estrogen decrease with depression, dysmenorrhea, sexual dysfunction and mineral bone loss. Bone loss in the elderly population leads to increased risk for osteoporosis and fractures. Hormonal replacement, however, not always revert symptoms, fact which favors the hypothesis that there are other pathophysiological mechanisms involved[29].

Sedation and cognitive disorders and myoclonus

Opioid-induced sedation and sleepiness may be related to its anticholinergic activity. Treatment includes diagnosing and treating comorbidities, dose interruption or reduction of other central nervous system depressants, opioid rotation, decrease the dose and use of psychic stimulants. In cancer patients in chronic use of opioids, methylphenidate (in dose between 10 and 20mg/day) may significantly increase psychomotor activity scores in up to 35% and sleepiness in up to 61% as compared to placebo. In addition, methylphenidate may decrease pain and rescue doses. Other less used agents are dextroamphetamine (2-20 mg/day), caffeine, donepezil and madafinil[30]. Statements and recommendations about this subject are shown in table 7[31].

Sleep disorders

Opioids also change the sleep and wake relationship, decrease total sleep time and efficiency, delta waves and REM sleep. It

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is possible that opioids change the dynamics of neurotransmitter circuits which regulate impulses converging to brainstem and those coming from pontinecholinergic projections. Morphine seems to regulate acetylcholine release in the reticular formation of the pons through the activation of the GABAergic pathway[32]. A study with cancer patients under morphine or methadone has shown that there has been only decrease of sleep timing stages 3 and 4, and increase in superficial sleep timing in almost 50%[33].

Psychomotor activity

During early treatment with opioids the ability to handle heavy equipment or to drive vehicles may be impaired. This, however, does not occur with patients who have reached stable doses of such agents. So, one cannot prohibit patients of performing their motor function; however care is recommended in early treatment stage[34].

Respiratory depression

The incidence of respiratory depression is low (0.002-1.2%) and there are few reports in the literature with the chronic use of opioids. Tolerance to this adverse effect is developed in a few days. On the other hand, the risk is increased for patients with sleep apnea, morbid obesity and chronic obstructive pulmonary disease (COPD). From 140 patients with chronic pain and using opioids, who were submitted to polysomnography, 75% had obstructive sleep apnea with significantly higher rates as compared to general population (2-4%)[35]. This has also been related to daily methadone dose associated to a benzodiazepine.

In reference studies, for the venous route, with self-controlled analgesia pump, the incidence of bradypnea is approximately 1.6% and of hypoxia of 15.2%. For the epidural route it is between 0.2% and 1.6% and for the subarachnoid route between 0% and 3%[36]. However, the association with drugs depressing the central nervous system (benzodiazepines, alcohol, inhalational anesthetics, tricyclic antidepressants, anti-histamines, IMAO, clonidine and neuroleptics) should be avoided. Such associations may lead to higher risk of respiratory depression. Also, when using any opioid, dose should be titrated according to patients' need and the type of aggressive stimulation, to avoid using doses above those necessary. It is important to inform patients that minimum effective dose to reach analgesia without adverse effects may be used progressively and that additional doses shall be used to reach the desired effect. So, to treat respiratory depression it is recommended: dose titration and reduction, use of opioid antagonist (intravenous 1–5µg/kg or 5µg/kg/h naloxone). On the other hand, buprenorphine-induced respiratory depression is only reverted by doxapram (IV 0.5-1.5 mg/kg every 5 minutes, maximum dose 2 mg/kg)[37]. Statements and recommendations for respiratory depression are shown in tables 5 and 6[38-43].

Pruritus

Mechanisms involved with opioid-induced pruritus genesis seem to involve the excitation of µ receptors in neurons not related to nociception and in motor neurons related to withdrawal reactions. It is possible that pain and pruritus are controlled by similar mechanisms or that pruritus represents a specific type of pain because both evoke motor responses (re-

Table 5. Statements based on clinical trials about opioid-induced sedation and respiratory depression

Sedation is a common opioid adverse effect, being more frequent in the first 24h of therapy (exception: methadone) and is directly related to dose increase.
Often, deep sedation represents a higher risk of respiratory depression and, in general, comes before it. It should be faced as risk index for respiratory depression.
Respiratory depression with deep sedation is a rare, however fatal, complication of the use of opioids, which imposes strict monitoring of breathing and consciousness level.
Studies have shown that 36% of patients had obstructive sleep apnea, 24% had central sleep apnea and 21% mixed disorder.
Fear of respiratory depression is a major limiting factor to effective analgesia, being responsible for pain undertreatment. The use of oral opioids in chronic pain patients is seldom associated to respiratory depression.
Although being a major complication, respiratory depression seldom evolves to death.
The use of opioid patient-controlled analgesia as compared to the traditional method presents similar adverse effects.

Table 6. Statements based on case reports and opinion of specialists for opioid-induced sedation and respiratory depression

For drug addicts, respiratory depression is the major cause of death.
The association of opioids with anesthetic drugs has synergic and additive effect for respiratory depression.
Respiratory depression is the most fatal secondary effect of the use of subarachnoid morphine (6 to 12h after administration).
Patients using spinal opioids should have ventilation (frequency and depth), oxygenation (SPO_2) and consciousness level monitored.
In most cases, respiratory and analgesic effects develop in parallel. Just one study suggests a potentially similar genetic basis for both.
Patients with central sleep apnea are at higher risk for respiratory depression when using opioids for analgesia.

Table 7. Recommendations based on clinical trials about opioid-induced cognitive disorders, sleepiness, delirium and behavioral disorders

Review and reduction, when possible, of prescription of psychotropic and central action drugs as measure to decrease opioid-induced delirium and sedation
Use of antipsychotics (especially those of high potency) to treat opioid-induced delirium or psychomotor agitation.
General clinical evaluation of patients with delirium to rule out other causes, such as adverse effects of non-opioid psychotropic drugs and latent infections.
In patients with delirium, perform behavioral measures for their treatment, such encouragement to regularize sleep-wake cycle, verbal comfort, prioritization of sleep quality and hygiene, and establishment of a quiet and relaxed place.
Education of patients and relatives about the situation to prevent falls, accidents and about operating heavy machines/driving when using opioids.
Modafinil or methylphenidate for opioid-induced sleepiness.
Drugs which may cause opioid-induced myoclonus: morphine, hydromorphone, fentanyl, methadone
Myoclonus control with 25% decrease in the opioid dose, opioid rotation, use of adjuvant analgesics, hydration and benzodiazepines is based on observational studies.
Cholinesterase inhibitors (donepezil) to fight opioid-induced sleepiness.

moval and scratching, respectively) which may be conducted by the same type of nervous fibers since no morphological differences were found between pain and pruritus receptors[44]. Pruritus may also be related to histamine release by mast cells. Fentanyl and sufentanil, however, may induce pruritus without histamine release. This effect occurs after administration by any route. Anti-histamines (diphenhydramine), ondansetron, opioid rotation, nalbuphin or naloxone may be used for treatment[45,46].

Nausea and vomiting

Their incidence is approximately 10-40%, however tolerance is rapidly developed (5-10 days). The mechanism is by activation of the chemoreceptor trigger zone, gastric stasis and increased vestibular system sensitivity. However, there are several other reasons for patients presenting such symptoms (other drugs, uremia, liver failure, hypercalcemia, increased intracranial pressure and gastrointestinal obstruction). Treatment includes reverting comorbidities and general measures such as: hydration, fractioned diet, oral hygiene, drug adjustment, use of other administration route different from oral, use of drugs. Recommendations of this article are shown in tables 8 and 9[47-50].

Abuse and addiction

When addressing abuse and addiction it is important to accurately define clinical syndromes (Table 1)[51]. A recent study has shown that the prevalence of addiction may vary from 0% to 31% (mean of 4.5%)[52]. On the other hand, the real prevalence of opioid-induced addiction is not known; however, it seems to be higher than expected and may vary from 0% to 50%[53,54]. This variation in prevalence may be due to differences in methods and risk factors when evaluating addiction, to treatment duration and to the observation of the study.

Table 8. Recommendations to treat nausea and vomiting based on clinical trials

Nausea and vomiting negatively impact the efficacy of the treatment with analgesics and are reason to abandon opioids.
Antiemetic drugs may be used as prophylaxis for nausea and vomiting.
Metoclopramide may be effective to treat opioid-induced nausea and vomiting.
Nausea and vomiting are decreased with the use of peripheral opioid antagonists.
Serotonin antagonists are effective to control vomiting.
Dopamine antagonists (including Chlorpromazine, levomepromazine, haloperidol and droperidol) help preventing nausea and vomiting.

Table 9. Recommendations to treat nausea and vomiting based on case reports and opinion of specialists

Antiemetic drugs may be used together with antipsychotics, prokinetic agents or serotonin antagonists.
Selective antagonist antiemetics of serotonin receptors may be indicated if nausea is severe or persistent.
Strategies to control nausea and vomiting should go beyond the administration of antiemetic drugs.
"Cold" food helps decreasing nausea discomfort.
Comfort measures, such as positioning, help preventing and treating nausea and vomiting.

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More common drugs looked for illicitly are oxycodone and hydrocodone in higher proportion than morphine, fentanyl and hydromorphone (25% of cases). On the other hand, among street users, methadone is the most widely used and sold drug[55].

Risk factors for opioids addiction and abuse include age (from 18 to 24 years of age), male gender, subjective pain complaint in different body regions, low back pain, previous history of alcohol abuse, Cannabis or illicit drugs, presence of psychiatric disorder (anxiety or depression) or of psychosocial stress, use of psychotropic drugs, increased level of tolerance to pain, eagerness to get the drug, criminal history, smoking, Caucasian race (for receiving more analgesics in emergency units), presence of pain-related functional limitation, history of post-traumatic stress, unemployment and hepatitis C (Table 10)[56,57].

With regard to genetic factors, variations in coding regions 118 A>G and 17 C>T SNP of the μ opioid receptor gene (OPRM1) and 36 G>T SNP of the OPRK1 receptor gene and 80 G>T and 921 C>T for the OPRD1 gene may increase the risk of abuse. Another polymorphism of pre and pro-encephalin (PENK) and of melanocortin type 2 receptor (MC2R) is associated to opioid addiction in several studies[58].

The use of tests to identify the potential for opioid addiction and abuse should be according to risk stratification: 1) low risk, no history of substance abuse or psychiatric comorbidity (DSM4); 2) medium risk, history of substance abuse or of psychiatric comorbidities (DSM4); 3) high risk, history of dependence and aberrant behavior (theft of prescription, falsification of prescription, injectable use of oral substances, alcohol abuse, aggressively requesting prescription, multiple entries in emergency units, loss of job, family and social life position)[59-61]. The chance of developing opioid abuse increases as individuals present more than one risk factor and positive toxicological urine tests are more frequent[62].

These questionnaires are still not validated in Brazil, have poor psychometric properties and are not reproducible, which implies methodological limitations with no basis for the good clinical practice. In addition, some are complex, extensive and poorly understood by patients. This way, when choosing a tool, one should think about easiness and application time, about physicians' skills to deal with the questionnaire and about patients' clinical characteristics. Self-report tools fail to identify aberrant behaviors[63].

Urinary tests may detect the presence of illicit drugs, such as heroin and cocaine, or of other controlled substances not prescribed by the physician. One should remind that 1 out of 5 patients using opioids have positive urinary test with regard to an illicit drug. Urinary tests help detecting substance addiction and abuse in 19.6% of patients. However, they may be false-positive and their use is not a routine[64].

Treatment of addiction is multidisciplinary, focused on specialized psychological support. Drug therapy includes the use of agonists (buprenorphine or methadone) or of an antagonist (naltrexone). The objective is to prevent or decrease physical dependence, eagerness and relapse and to return all physiological functions (such as sleep and bowel movements) to normal.

One should be careful with the risk of drug interaction, of diversion and overdose potential. Buprenorphine, as opposed to methadone, does not induce electrocardiographic alterations or erectile, cognitive and psychomotor dysfunction. However, its approximate cost is 12 dollars/day and has ceiling effect. Methadone should be started with doses below 40 mg and is the first choice for pregnant patients. However, it poses higher risk for arrhythmia, overdose, weight gain, sedation and relapse after 12 months of treatment. Naltrexone should be started seven days after opioid withdrawal, treating withdrawal syndrome with clonidine. Table 12 shows some drugs to treat addiction[65].

Table 10. Concepts used in the clinical practice. Adapted[58]

Tolerance	Adaptation stage where the exposure to a drug induces alterations resulting in reduction of effect of one or more opioids along time.
Physical addiction	Adaptation stage characterized by withdrawal syndrome, which may result from abrupt withdrawal, from fast dose decrease or from blood concentration of a drug or from the administration of specific antagonist.
Addiction	Chronic and primary neurobiological disease the development and manifestation of which are associated to genetic, psychosocial and environmental components. It is characterized by behaviors which include lack of control of the use of the drug, compulsive use, eagerness and continuous use regardless of the harm the drug produces.
Aberrant behavior	Behaviors that go beyond limits agreed in the treatment plan between physician and patient.
Misuse	Use of drug without medical indication or for other reasons different from those prescribed. It also involves the use of substances (intentional or not) in incompatibility with medical recommendations. There may be alteration of doses or drugs breakdown with harmful consequences for individuals.
Abuse	It is misuse, with consequences, to change or control behavior or mental status in illegal or noxious manner of oneself or of others. This includes accidents, insults, legal problems, and sexual behavior which increases the risk of acquiring sexually transmissible diseases.
Diversion	This is the intentional transfer of substances from a legitimate distribution to illegal channels or the acquisition of drugs by illicit means.

Table 11. Opioid addiction: red flag to have in mind. Adapted[54]

There is opioid addiction suspicion in patients who:
1. Describe back pain or pain resulting from orthopedic injuries without correct documentation or image.
2. Ask for a specific type of opioid for pain relief.
3. Show little interest in performing clinical exams, diagnostic tests and non-pharmacological treatments.
4. Talk about changes in job or related situations.
5. Stop participating in activities which before would occupy a large part of their time. This may be a signal of social isolation or of the need for time to look for opioids.

Table 12. Drugs used to treat opioid addiction. Adapted[66]

Drugs	Action	Indication	Dose	Frequency
Buprenorphine	Partial opioid agonist	Withdrawal and maintenance	2-32mg sublingual	Once a day or three times a week
Clonidine	α2-adrenergic antagonist	Withdrawal	0,1-0,3mg oral	Every 6h
Levomethadyl acetate	Opioid agonist	Maintenance	25-100mg oral	Three times a week
Methadone	Opioid agonist	Withdrawal and maintenance	20-100mg oral	Once a day
Naltrexone	Opioid agonist	Withdrawal and maintenance	50-100mg oral	Once a day or three times a week

CONCLUSION

The use of opioids in the short or long term is not free from risks. Adequate patients' selection and supervised drug use help monitoring and managing adverse effects.

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