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Opioid Controversies in Chronic Non Cancer Pain

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Abstract

Opioids use for Chronic Non cancer Pain (CNCP) treatment has been increasing worldwide. Despite their important role for moderate to severe pain treatment, their use in CNCP has been subject of great controversy. Opioid long-term use is associated with adverse effects development such as hypogonadism, osteoporosis, immunosuppression, cognitive disorders, opioid induced hyperalgesia (OIH) and opioid addiction. Moreover, there is uncertainty about their long-term effectiveness and safety. It is important to raise awareness among physicians of opioid long-term effects, as well as, strategies for their prevention and treatment.

Keywords: Opioids; Chronic non cancer pain; Adverse effects; Long-term effectiveness; Safety

Introduction

Chronic Non Cancer Pain (CNCP) is a pain condition provoked by any non- cancer disease that persists continuous or intermittently for 3 or more months [1]. Opioids are one therapeutic option for CNCP treatment and their use has been increasing significantly in some countries [2,3]. Their usage has been associated with the development of side effects such as nausea and vomiting, constipation, sedation, itching and respiratory depression by overdose [4,5]. Some of these side effects tend to decrease over time and there are several therapeutic options to decrease its incidence and intensity.

Opioids use in CNCP treatment has been subject of great controversy because of their potential to develop side effects and limited evidence of their long-term effectiveness [2,3,6,7]. As far to our knowledge, the published trials on the effectiveness of opioid drugs have several methodological issues such as short follow-up periods, loss to follow up or reduced statistical power [2,8-11]. A systematic review published by Kalso et al., highlighted the short-term effectiveness (3 months) of opioids although its use was associated with a high prevalence of adverse reactions (80% opioid vs placebo 56%). This review also reported a high discontinuation of opioid therapy in their long term use [8]. The review published by Noble et al. also supports the limited evidence of the effectiveness on long-term use of opioid therapy and identifies as the main causes of their discontinuation their limited long –term analgesic efficacy and side effects development [10]. Chou et al., showed no differences in safety or effectiveness of long-acting opioids, as well as, in the comparison of the long-acting to short-acting opioids [12]. Therefore, there is still great controversy about effectiveness and safety of opioids in CNCP. More prospective observational studies are needed with longer follow-up times and with evaluation of functional recovery degree and quality of life of these patients.

According to IMMPACT recommendations, a given therapeutic's effectiveness should always be assessed taking into account at least 2 of the following areas: intensity of pain, physical functioning, emotional functioning and overall assessment of the patient's condition [13]. A trial with a sample of 1144 CNCP patients on long-term therapy with opioids, showed that the patients who reported greater psychosocial impact, were patients with higher levels of depression. These findings were not related to the intensity of pain or with its chronicity, raising the importance of psychosocial assessment of these patients [14].

In several countries; the increased opioid prescription in CNCP led to the regulation and monitoring of its use and increased awareness about their potential long-term adverse effects [15-17]. Opioid long term effects include neuroendocrine system dysfunction, osteoporosis, immunosuppression, cognitive disorders, opioid-induced hyperalgesia and addition. There is no consensus on the relationship between opioid dose and risk of developing these effects. However, risk increases with higher doses and with longer periods of exposure. According to some recommendations, opioids should be titrated to maximum daily doses of 90-120 mg/day of oral morphine or equivalent [18]. If higher doses are needed, patient should be referred to a Chronic Pain Center. All guidelines alert for overdose and respiratory depression risk when doses higher than 200 mg per day of oral morphine or equivalent are used [4,7,15,18,19].

Despite the lack of evidence about effectiveness and safety of opioid long term use, all treatment guidelines of CNCP keep formal indication for their use in moderate to severe pain [7,16,18,20]. Therefore, it is important to raise clinician´s awareness about side effects induced by long-term opioid prescription and their repercussion in functional recovery and quality of life of these patients.

Opioid induced androgen deficiency (OIAD)

Opioid induced Androgen deficiency (OIAD) is a syndrome characterized by decreased levels of gonadotropic hormones (FSH,

LH) with consequent reduction in sexual hormones (such as testosterone). The effect of opioids in the hypothalamus-pituitary axis consists in gonadotropin-releasing hormone inhibition at the hypothalamus level and seems to occur only a few hours after beginning drug administration [21]. Some animal trials show the peripheral effect of opioids with the increased expression of enzymes such as 5-alpha reductase type 1 and P-450 aromatase whose catalytic action contributes to the reduction of testosterone levels in OIAD [22]. Clinically, OIAD is characterized by infertility, decreased libido, male erectile dysfunction, female menstrual dysregulation, galactorrhoea, fatigue, depression, body hair loss, osteoporosis, muscle mass loss, obesity and anemia. The OIAD affects equally both genders. A case control study of 40 patients who survived from cancer revealed that 90% of patients under opioid treatment developed OIAD compared with only 40% in control group [23]. Monitoring clinical signs and symptoms of this syndrome is essential and there are some clinical tools available to help in the diagnosis of this syndrome [24]. Current recommendations for patients under long term use of opioids advise regular clinical assessment of signs and symptoms and hormonal assays. In patients with OIAD, shifting for a new analgesic regimen without opioids or hormone replacement therapy should be considered [21,25]. A randomized controlled trial conducted over 14 weeks in patients on opioid therapy for CNCP, showed that the group who underwent hormone replacement therapy with testosterone had increased tolerance to mechanical noxious stimuli or stress, improved libido and increased muscle mass [26].

Osteoporosis and bone fracture risk

Osteoporosis is one of OIAD consequences, but it only explains partially the increased fracture risk found in these patients. A study by Fortin et al. which included 81 men on opioid therapy during weeks to years of follow-up, found no correlation between the results of bone mineral density and reduced testosterone levels [27]. Opioids seem to have a direct inhibitory action over osteoblast as evidenced by the decrease in osteocalcin production seen in these patients. Therefore, they have a reduction in bone mineral density and an increased risk of bone fracture [28,29]. On the other hand, it is important to consider the potential effects of opioid medications concerning to cognition and alertness, which may also contribute to an increased risk of falls [5,28].

Immunosuppression

Pain is associated with activation of hypothalamic-pituitary-adrenal axis neuroendocrine system activation and an associated immunosuppression risk. The immunomodulation effect of opioids is still unknown; however, it was reported in some experimental trials with animals.

Opioid´s use in chronic pain seems to play a central inhibitory effect of hypothalamic-pituitary-adrenal axis with decreased production of corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). Moreover, peripheral MOP receptors on lymphocyte populations can be hypothetical mechanisms responsible for immunosuppression risk in patients on opioid therapy. Researches in mice lymphocyte MOP receptors knock-out, did not show any immunosuppression following opioid exposure [30]. More studies are needed to evaluate clinical relevance of immunosuppression induced by bopioids [5,30,31].

Accordingly with some animal trials, this effect seems to be higher with Codeine, Fentanyl, Morphine, Methadone and Remifentanil. On the other hand, this immunosuppressive response appears to be virtually nonexistent with Buprenorphine [30]. Therefore, opioid therapy for CNCP should use the clinically lowest effective dose, during the shortest possible period of time and using opioids with an apparent lower immunosuppressive action such as Buprenorphine [28].

Cognitive Dysfunction

The use long-term use of opioids may induce cognitive impairment such as decreased concentration ability, deficits in processing information and memory, difficulty in problem solving or completeness of tasks, confusion, disorientation and psychomotor slowing [32]. Multiple studies have been published about this potential correlation. Nevertheless, due to methodological insufficiencies there are no established recommendations [5,32]. Beyond this, Chronic pain can itself be a risk factor for cognitive disability development. McCracken et al. studied a population of 257 patients with chronic pain and concluded that 80.6% of patients had 3 or more cognitive dysfunctions. In this trial, depression was identified as a risk factor for cognitive impairment [33]. The results of a systematic review carried out in 2010 about the potential association of opioids with cognitive impairment are inconclusive. However, the authors recommend that despite these results, it is important to alert patients and clinicians about this potential risk [32].

In clinical practice it is important to note that several other factors may contribute to the development of cognitive disorders such as advanced age, chronic pain, pain intensity, high opioid doses or co-morbidities. Therefore, it is important to regularly monitor these patients and apply neuropsychological screening tests. In this context, despite its low sensitivity for mild cognitive changes, the Mini-Mental State Examination test appears to be a useful tool and easy to apply in clinical practice.

Opioid cognitive effects are of major importance concerning the ability of these patients to drive or participate in potentially hazardous activities. In this context, the results of several studies are inconclusive and should be interpreted with caution. On the other hand, a patient with pain has cognitive disorders that may interfere significantly in their ability to drive [34]. Thus, in the clinical decision about the drive ability, all the possible factors that might interfere with cognitive and psychomotor skills should be considered, such as intense pain (Numerical Pain Scale ≥ 7), sleep disturbances/ daytime sleepiness, concomitant sedative drugs usage (benzodiazepines, tricyclic antidepressants, anticonvulsants, antihistamines, anticholinergics) or short- acting opioids for breakthrough pain [16].

As a public health measure and to safeguard patients safety, clinicians should recommend a ban on driving or performing hazardous tasks for patients who are starting opioid therapy or titrating doses until a stable dose is achieved, and for patients with clinical signs of sedation or cognitive disorders [19]. Patients are not allowed to drive if on opioid therapy and association with alcohol, benzodiazepines or other sedative drugs [16]. Therefore, patients on stable therapy are enabled to drive if properly monitored by their doctor [35,36].

Opioid-induced hyperalgesia

The opioid induced hyperalgesia (OIH) is a central sensitization state that leads to a decreased pain threshold to nociceptive stimuli in patients exposed to opioid drugs and may be a cause of their long-term limited effectiveness [5,37-39]. The exact mechanism of OIH has not

yet been fully clarified. Several animal studies have shown the association of hyperalgesia development with opioid exposure [37,40]. However, in humans there is not enough evidence to support or refute the OIH, with the exception of few reports including experimental healthy volunteers opioid´s exposition [39,40]. There is also not enough evidence regarding the association of opioid perioperative use and increased postoperative pain and analgesic requirements. Some articles argue that chronic use of large doses of opioids may be a potential risk factor [40,41]. In a recently published systematic review, Rivosecchi et al. advocate that hyperalgesia associated with Remifentanil infusions has little clinical expression and, therefore, the systematic application of preventive measures are not needed [40].

Some of the mechanisms that may be in OIH genesis are:

- Activation of the central glutaminergic system through NMDA stimulation receptors by opioids. The phosphorylation of these receptors induced by activation of kinase C protein leads to an increased uptake of calcium and contributes to central sensitization.

- Activation of descending pathways mediated by opioid action within the rostroventral medulla with spinal dynorphins release. Dynorphins have a pro-nociceptive action through direct stimulation of nociceptive afferent pathways.

-Increased release of excitatory neurotransmitters such as CGRP, substance P and cholecystokinin in rostroventral medulla (induced by spinal dynorphins) [39-42].

In OIH, pain is diffuse, intense and usually surpasses the original location of patient's pain. An important differential diagnosis to be considered in the clinical evaluation of these patients is opioid tolerance. Opioids tolerance is characterized by a progressive loss of efficacy with higher doses needed to achieve analgesia. Unlike the latter, OIH is characterized by progressive loss of analgesia or even worsening of pain with increasing opioid doses. Although pharmacologically distinct, clinically may be hard to distinguish both [37,39,42].

OIH treatment is a clinical challenge. The main preventative strategies consist in use the lowest effective opioid dose, adjuvant therapy or non-pharmacological techniques. Main treatment options involve dose reduction or even opioid discontinuation; shifting to partial opioid receptors agonists (Buprenorphine); usage of other analgesics such as COX-2 nonsteroidal anti-inflammatory (NSAIDs) drugs, NMDA antagonists (Ketamine) or even consider judicious usage of Methadone [19, 39,40,42,43].

Opioid misuse, Abuse and Addiction

Opioid abuse and addiction risk is related to analgesic and euphoric properties of these drugs [14,44,45]. Opioid misuse concerns to contrary use of these drug´s prescription regardless risk of harmful effects. Opioid abuse consists in their intentional use for recreational purposes (euphoria or altering state of consciousness).

Patients under opioid therapy can develop drug abuse behaviors and manifest withdrawal signs and symptoms with its discontinuance or dosage reduction [45-47]. According to Portenoy et al., addiction is a psychological and behavioral syndrome characterized by physical dependence, compulsive search of a drug and aberrant behaviors related with their use [17,48]. Misuse prevalence ranges from 21% to 29% and the addition estimated prevalence ranges from 0% to 12 %[45].

The transition from physical dependence to addiction appears to be associated with learning and memory mechanisms [44]. Its pathogenesis should be assessed taking into account neurobiological factors including reward circuitry activation and learning behaviors involving structures such as the amygdala, hippocampus and cerebral cortex. Nevertheless, genetic factors involving opioid drug metabolism and transport variability medications, as well as, social and environmental factors (personal history of tobacco, alcohol, benzodiazepines or illicit drugs abuse, peer pressure, social factors or unemployment) are also considered potential risk factors for its development [46,49,50]. Mackey et al. published a trial about gray substance volume decrease in right amygdala integrating the reward and brain learning circuitry, in a sample of 10 patients under morphine medication for 1 month because of lumbar back pain. These brain changes were reversible with opioid withdrawal in 4.7 months of follow-up [51].

Opioid addiction diagnosis is difficult and it depends on subjectivity inherent to clinical evaluation. However, a detailed clinical history and physical examination with potential risk factors evaluation, use of validated assessment tools and regular monitoring of patients on opioid chronic therapy appears to be the best strategy to reduce the risk of opioid addiction. For its prevention, guidelines recommend usage of lowest clinically effective dose, during the shortest period of time and under physician supervision [15,49,52]. Opioid addiction treatment includes shifting to methadone or buprenorphine, monitoring high-risk patients with urine tests, supervision of medication (number of pills and boxes) and opioid withdrawal under medical supervision [16,49].

Conclusion

Opioids are clinically relevant therapeutic options in moderate and intense pain treatment [2,6,15,17]. Their use in CNCP has increased in recent years albeit the controversy given the limited evidence of its long-term effectiveness and its potential to develop adverse events such as hypogonadism, osteoporosis, increased risk of fractures, immunosuppression, cognitive dysfunction, opioid-induced hyperalgesia and addiction risk [5,53,54].

Knowledge about mechanisms involved in the development of these adverse effects, as well as, the available therapeutic options for their prevention or treatment are of crucial importance. Parallel to the development of opioid adverse effects, some studies have demonstrated limited effectiveness and functional recovery, which raises serious questions about its applicability [7,8,15,16,20].

Despite these facts, the methodological shortcomings in the various studies namely the reduced follow-up times and high rates of discontinuation, do not allow the degree of evidence needed to make recommendations in this context [8-10,17,20,47]. Currently, several guidelines recognize the important therapeutic role of these agents in patients with CNCP, which led to a significant increase in the prescription of such drugs in some European countries and the United States [2,15,16,20]. Therefore, it is important to raise awareness among physicians about the potential risk of adverse effects induced by these drugs, as well as, their limited long-term effectiveness, functional recovery and impact on quality of life of these patients. Appropriate selection and monitoring seem to be the best option in order to ensure opioid effectiveness and safety in CNCP.

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