An update on the role of opioids in the management of chronic pain of nonmalignant origin

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Purpose of review

To summarize and reflect over primarily recent epidemiological and randomized controlled trials in opioid-treated chronic nonmalignant pain patients, focusing on effects, side effects, risks and long-term consequences of the treatment.

Recent findings

In the western world opioids are increasingly being used for long-term treatment of chronic nonmalignant pain. While the long-term benefits of opioids regarding pain relief, functional capacity and health-related quality of life still remain to be proven, studies are emerging that describe serious long-term consequences such as addiction, opioid-induced hyperalgesia, cognitive disorders, and suppression of the immune and reproductive systems.

Summary

Much more research is needed concerning long-time effects and consequences of opioid therapy in chronic nonmalignant pain patients; however, some clear warning signals have been sent out within recent years.

Keywords

chronic nonmalignant pain, epidemiology, opioid, side effects

Curr Opin Anaesthesiol 20:451–455. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Anaesthesiology 2007, 20:451–455

Abbreviation

OIH opioid-induced hyperalgesia

0952-7907

Introduction

Randomized controlled studies of long-term opioid treatment in chronic nonmalignant pain patients are generally of short duration [1•], and long-term follow-up studies are few and often carried out in meticulously selected patients [2•]. To assess the broader role, we must also turn to population-based epidemiological studies [3,4••].

Caution about opioid treatment of chronic pain has long been based on fear of addiction and diversion [4••]. Other potentially and extremely important clinical issues such as physical dependency, tolerance development, cognitive disorders, abnormal pain sensitivity, and dysfunction of the immune and reproductive systems may, however, give rise to concerns [5••,6]. Guidelines for responsible use of opioids in chronic nonmalignant pain conditions reflect concerns over these problems [7,8,9••].

Epidemiology of opioid use

Even in the western world the prevalence of chronic nonmalignant pain conditions varies dramatically between countries depending on the applied definitions of chronic pain as well as different assessment tools and study populations [10]. Likewise, the consumption of opioids in chronic nonmalignant pain populations varies primarily depending on the regulations regarding opioid prescribing. We have chosen to describe the epidemiology of long-term opioid therapy in chronic nonmalignant pain patients from data coming out of Denmark for four reasons. (1) The data from Denmark including opioid use are quite unique due to comprehensive and accurate healthcare statistics and databases. (2) Denmark is not yet constrained by an unmonitored private sector or by privacy sensibilities. (3) Denmark has one of the highest per capita consumptions of prescribed opioids worldwide, with an estimate of 67% of this being used to treat chronic pain of nonmalignant origin. (4) In many western countries the development of legal opioid consumption for chronic pain is moving in the same direction as in Denmark [11–13]. During the last two decades the use of opioids for the treatment of chronic noncancer pain has increased considerably in the western world, exemplified by the more than 600% increase in Denmark [14].

Every 6 or 7 years in Denmark, a cohort of adults is randomly selected from the Danish Central Personal Register and asked to participate in a Health and Morbidity Survey.

Through face-to-face interviews and postal questionnaires, including a quality of life assessment (Short Form-36), a wealth of data is provided. In the survey from the year 2000, 10 066 individuals participated, 1906 of whom were identified as suffering chronic nonmalignant pain (longer than 6 months). An overall chronic nonmalignant pain prevalence of 19% was found: 16% for men and 21% for women [3]. Nearly 130 000 of the Danish population used opioids on a continuous or regular basis. Opioids were used regularly or continuously by 12% of those persons who suffered from chronic pain: 3% used the so-called 'strong' opioids and 9% used the 'weak' opioids (tramadol, codeine and dextropropoxyphene). A further analysis of users of 'weak' and 'strong' opioids was not provided in this study. Prevalence of opioid use was 20% among those who reported moderate/severe or very severe pain, compared with 3% among those who reported none/very mild or mild pain. Prevalence of opioid use among those who reported fair, bad or really bad self-perceived health was 18% compared with 4% among those who rated their health as really good or good. Among individuals suffering from chronic pain, opioid usage was significantly associated with reporting of moderate/severe or very severe pain, poor self-rated health, lower quality of life scores and living alone (being separated/divorced or widowed). In addition, significant associations between opioid use and low levels of physical activity and employment, and high levels of healthcare utilization were identified [3]. Due to the cross-sectional design of the epidemiological studies, causation is not proven and the possibility that the group of opioid users could be worse off without opioid treatment cannot be excluded. It does seem, however, that opioid treatment of chronic pain as currently provided, and when assessed across an entire population, is not achieving the key goals recommended by the guidelines [7,8,9••]: pain relief, improved functional capacity and quality of life.

Efficacy of opioids

A recent meta-analysis of effectiveness and side effects of oral opioids for chronic nonmalignant pain conditions only including randomized controlled trials showed that opioids reduced pain and improved functional capacity better than placebo. Trials with parallel groups were longer than those of crossover design (5.6 vs. 3.8 weeks, on average). Treatment duration also varied according to pain condition. Thus, durations of opioid therapy during the studies of fibromyalgia and mixed types of pain (mean duration: 8.8 and 8.5 weeks, respectively) were about twice as long as those involving patients with nociceptive and neuropathic pain (mean duration: 4.8 and 4.3 weeks, respectively). The average dropout rate was 38%: 30% because of insufficient pain relief and 10% because of side effects. Ninety percent of the studies were either funded by or had one or more coauthors affiliated with the pharmaceutical industry [1•].

Chronic pain is a long-term disorder. The studies included in the above-mentioned meta-analysis had various follow-up periods; most trials were not long enough to estimate the duration of efficacy of opioids in chronic pain, the potential for opioid tolerance and the long-term consequences of opioid use.

Side effects

Two systematic reviews have recently assessed side effects in chronic nonmalignant pain patients treated with opioids [1•,15]. Moore and McQuay [15] found that even in relatively short-term trials about half of the patients experienced side effects from opioids and that 20% of the patients discontinued opioid treatment because of side effects. The most common side effects were nausea or vomiting, constipation, drowsiness or dizziness, dry mouth, dry skin and pruritus. The frequency of side effects seems to be much higher in patients using opioids on a daily and continuous basis than in patients using opioids on intermittent basis [16•].

Long-term consequences

Apart from conventional side effects, long-term opioid treatment may also have other much more serious consequences, which should particularly be considered in patients with chronic nonmalignant pain conditions due to their often normal life expectancy.

Physical dependence is a state of adaptation that is manifested by a specific drug class, e.g. opioids. Withdrawal symptoms can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist [17]. The most important symptoms of withdrawal in opioid-treated pain patients are increased preexisting pain, deep bone pain and diffuse muscles aches [18,19]. Chronic pain patients who frequently use supplemental short-acting opioids on demand may become physically dependent and develop intermittent withdrawal symptoms [20]. End-of-dose failure, i.e. when pain occurs or is markedly worsened at the end of an opioid dosing interval, seems to be a frequent cause for breakthrough pains [21,22,23•].

Tolerance may be involved when the opioid dose has to be increased in order to maintain a certain level of pain relief. In a 10-year follow-up of opioid-treated chronic pain patients, tolerance was not a problem in the majority of patients [24•]; however, dose escalation had occurred in a minority of patients. Two patients increased opioid doses from 30 and 67.5 to 1080 mg and one patient increased the dose from 450 to 1140 mg. Mystakidou *et al.* [25] followed chronic nonmalignant pain patients on transdermal fentanyl and found that doses escalated from 75 or less up to 250 μg/h within a period of 18 months. In a retrospective survey of 104 chronic pain patients younger than 50 years and 102 patients older than 60 years, Buntin-Mushock *et al.*

[26] found that both groups had increased the opioid doses over the 15-month period. The younger patients increased the doses with an average equivalent of 27 mg of daily oral morphine monthly, while the older patients increased the doses with an average equivalent of 12 mg of daily morphine monthly. In the younger patients with nociceptive pain the dose escalation was much higher (equivalent of 38 mg of daily morphine monthly) than in the younger patients with neuropathic pain (equivalent of 16 mg of daily morphine monthly). Thus, the development of tolerance may be dependent on age and type of pain. Another worrying finding of this study was that although the younger patients had a dose increase of 640% (from 49 to 365 mg/daily) during the observation period, the pain visual analogue scale scores did not change at all.

Addiction is a psychological and behavioral syndrome characterized by evidence of psychological dependence, evidence of compulsive drug use and/or evidence of other aberrant drug-related behaviors [27,28]. In a recent literature review [5••] the prevalence of addiction was found to vary between 0 and 50% in chronic nonmalignant pain patients depending on the diagnostic criteria. The most commonly abused opioids are oxycodone, hydrocodone, hydromorphone, methadone and morphine [29••]. The rush the person experiences after administration of a drug is caused by a rapid and large increase in dopamine in the brain reward system, and important factors for abuse liability associated with the drug include the speed of access and the concentration at the target sites. On a newly developed scale of opioid attractiveness [30•], sustained-release oxycodone had the highest and the fentanyl patch the lowest score. Oral transmucosal fentanyl citrate, methadone and sustained-release morphine had scores in the middle of the scale. Risk factors for opioid abuse associated with chronic nonmalignant pain patients are young age, male gender, past alcohol or cocaine abuse, previous drug conviction [31•], mental health disorders [32•], pain in multiple regions and pain after motor vehicle accidents [33•]. Meticulous adherence monitoring of chronic nonmalignant pain patients on opioids in a multidisciplinary pain center involving the pharmacies and all other treating physicians resulted in a 50% reduction of opioid abuse [34•].

Recent studies in animals and human have suggested that under certain circumstances opioids may produce opioid-induced hyperalgesia (OIH). In humans, experimental studies in former opioid addicts maintained on methadone, in patients undergoing surgery and in experimental pain studies on volunteers have indicated that OIH may be a generalized and quite frequent phenomenon [35••]. Animal studies have suggested a number of underlying mechanisms including enhanced excitatory amino acid neurotransmitter availability and receptor sensitivity, enhanced release of dynorphine in the dorsal horn, activation of descending pain facilitation mechanisms in the rostral ventromedial medulla, and increased calcitonin gene-related peptide and substance P expression in the dorsal root ganglion [35••,36]. Celerier *et al.* [37] have recently proposed a model of the neuroadaptive changes in which the antinociceptive system and the pronociceptive system are in balance at a low levels of neuronal activity before the exposure of opioids. After opioid exposure the pronociceptive system becomes upregulated, reflecting development of OIH. When opioids are discontinued, the antinociceptive system is upregulated and the OIH is resolved; however, the recovery of OIH is the result of a new equilibrium between the two systems, which occurs on a higher level of neuronal activity. This high-level balance may be prone to dearrangements, which in the clinical context may form the basis for an increased vulnerability to pain. A retrospective study in chronic nonmalignant pain patients undergoing detoxification from high doses of opioids indicated the presence of OIH, as the majority of the patients reported significant pain relief after detoxification [38•].

A feared side effect as well as a long-term consequence is that opioids may cause cognitive dysfunction [39,40]. We have found impaired neuropsychological performance regarding reaction times, psychomotor speed and working memory in opioid-treated chronic pain patients compared to healthy volunteers. As the control group consisted of healthy individuals and not patients with chronic pain not taking opioids, other factors may influence the results considerably. Interestingly, the patients receiving methadone performed significantly slower regarding psychomotor speed compared with patients treated with equianalgesic doses of sustained-release morphine [39]. This finding may indicate that the type of opioid may also play a role in the cognitive function during long-term treatment. In a more recent study, an untreated group of chronic pain patients participated. This study indicated that the opioid-treated patients performed poorer on a test of working memory than the nonmedicated patients [39,40]. This area needs much more research, however, as many other factors may play a role in cognitive dysfunction in these patients, e.g. pain itself, psychosocial comorbidities etc.

Opioids have inhibitory effects on both the humoral and cellular immune system by directly binding to μ-receptors present on the immune cells [41] and μ-receptors within the central nervous system [42••]. The central effect of opioids is activation of the descending pathways of the hypothalamic–pituitary–adrenal axis, which elicits the production of glucocorticoids, and the sympathic nervous system, which elicits the release of noradrenalin [43]. Both glucocorticoids and noradrenalin act on lymphocytes

by suppressing the immune capability. The effect of the immunosuppression by opioids has been shown to accelerate onset of acquired immunodeficiency syndrome in animals [44], modulate lymphocyte function following Bacille Calmette–Guérin vaccination in pigs [45] and contribute to the development of infections in burn patients [46]. Animal studies have shown that different opioids do not share the same immunosuppressive effects. Opioids with a high immunosuppressive capacity include codeine, methadone, morphine, remifentanyl and fentanyl, whereas hydromorphone, oxycodone and tramadol seem to be less suppressive. Buprenorphine seems to be devoid of immunosuppressive effects [42••] and may even play a protective role against the metastatic diffusion following cancer surgery [47].

Hypogonadism in both men and women receiving opioids for chronic nonmalignant pain has previously been documented, especially in patients receiving intrathecal opioids [48•]. In men with opioid-induced androgen deficiency, treatment with a testosterone patch normalized hormone levels, and improved sexual function, mood, depression and hematocrit levels [49]. It has also been shown that opioids have varying effects on the activity of human placental aromatase cytochrome P450 19, which is a key enzyme in the biosynthesis of estrogens by the human placenta. Oxycodone and codeine had no effect on aromatase activity, whereas morphine and hydromorphone among others increased the activity. The effects of opioid treatment during pregnancy are still not ruled out [50].

Methadone may produce prolongation of the QT interval corrected for heart rate both in drug abusers in maintenance treatment with methadone [51] and in chronic pain patients [52,53], but in chronic pain patients the risk of serious arrhythmias seems to be small [52,53]. Buprenorphine does not significantly alter the corrected QT [54].

Conclusion

Opioids could be hypothesized to have relatively short-run benefits, which in the long-run may turn into opposite and deleterious effects. In a 'real-world' study of the Danish population opioid use did not fulfill any of the key outcomes recommended by guidelines: pain relief, improved functional capacity and quality of life. The fact that opioids can improve the key outcomes in selected patients with chronic nonmalignant pain should not be ignored. A whole range of very serious long-term risks and consequences are, however, beginning to emerge, such as addiction, tolerance, OIH, cognitive disorders, and suppression of the immune and reproductive systems. Much more research is needed regarding the long-term consequences of opioid therapy.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 495–496).

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