

Non-Analgesic Effects of Opioids: The Cognitive Effects of Opioids in Chronic Pain of Malignant and Non-Malignant Origin. An Update.

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Abstract: Opioids constitute the basis for pharmacological treatment of moderate to severe pain in cancer pain and non-cancer pain patients. Their action is mediated by the activation of opioid receptors, which integrates the pain modulation system with other effects in the central nervous system including cognition resulting in complex interactions between pain, opioids and cognition. The literature on this complexity is sparse and information regarding the cognitive effects of opioids in chronic pain patients is substantially lacking.

Two previous systematic reviews on cancer pain and non-cancer pain patients only using controlled studies were updated. Fourteen controlled studies on the cognitive effects of opioids in chronic non-cancer pain patients and eleven controlled studies in cancer pain patients were included and analyzed.

Opioid treatment involved slightly opposite outcomes in the two patient groups: no effects or worsening of cognitive function in cancer pain patients and no effect or improvements in the chronic non-cancer pain patients, however, due to methodological limitations and a huge variety of designs definite conclusions are difficult to draw from the studies. In studies of higher quality of evidence opioid induced deficits in cognitive functioning were associated with dose increase and the use of supplemental doses of opioids in cancer patients.

Future perspectives should comprise the conduction of high quality randomized controlled trials (RCTs) involving relevant control groups and validated neuropsychological assessments tools before and after opioid treatment in order to further explore the complex interaction between pain, opioids and cognition.

Keywords: Opioid, cognition, chronic pain, cancer pain, neuropsychological assessment, systematic review.

OPIOIDS, PAIN AND COGNITION

Opioids constitute the basis for pharmacological treatment of moderate to severe pain. Their action is mediated by the activation of opioid receptors, which integrate the pain modulation system with other actions on the CNS including cognition. It is well-known that the cognitive effects of opioids as well as other side effects are qualitatively and quantitatively different in opioid naïve individuals compared to individuals in long-term treatment [1]. This may be due to the development of tolerance and opioid-induced hyperalgesia [2].

There exists complex interactions between opioids, pain and cognition, which in cancer patients and patients with chronic non-cancer pain is further complicated by co-morbidities and psychosocial factors. Looking at the literature on the complex interactions between opioids, pain and cognition [3,4] including the literature on patients' complaints of cognitive dysfunction during opioid treatment [5], it is clear that opioids interfere with cognition in various ways. However, depending on the symptom load and clusters of physical as well as psychosocial symptoms and co-morbidities the cognitive effects of opioids may well be both deleterious and beneficial [6]. Currently, opioid analgesics are being increasingly prescribed to manage chronic pain of various etiologies, partly due to the widespread knowledge regarding their beneficial effects in cancer pain [7] and, partly due to lack of alternatives to manage chronic non-cancer pain [8]. However, in both populations information regarding their effects on cognitive function is substantially lacking.

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Cognition has been described as the brain's acquisition, processing, storage and retrieval of information [9]. Cognitive function involves mental processes associated with receptive functions (select, acquire, classify and integrate information), memory and learning (information retrieval and recall), thinking (mental organization and re-organization) and expressive function (communication and comprehension) [10]. Dysfunction of any or all of these abilities can fundamentally impact all aspects of life. In the health care setting cognitive dysfunction are likely to reduce comprehension of and compliance with treatments, expose patients to risks, make the disease more difficult to manage, cause distress to family and potentially reduce quality of care. These are complicated issues, which may affect a large number of patients. Thus, use of opioids have been associated with accidents [11-13] and long-term opioid use may even cause premature death [14].

The aim of this review is to describe the cognitive effects of chronic non-cancer and cancer pain and by reviewing the literature systematically including only controlled studies in order to extract the cognitive effects of opioids in chronic non-cancer and cancer pain conditions.

COGNITIVE FUNCTION AND CHRONIC NON-CANCER PAIN

In the clinic, cognitive function may be assessed by different neuropsychological tests measuring executive functions of different domains of cognition as attention, concentration, reaction time, vigilance, working memory, verbal memory, and motor coordination. A brief description of the most commonly used tests has been given by Ersek *et al.* [15] and Kurita *et al.* [3]. Their combination with anatomical, functional, and chemical neuroimaging have provided new opportunities for a better understanding of chronic pain,

and neuroimaging studies have claimed that chronic pain is a disease of the brain [16]. Many patients with chronic pain often complain of attention and memory problems, but the neural substrates of the interaction between pain and cognition are still not well understood. It has been postulated that pain modulates an attention-specific network that includes the dorsolateral and medioprefrontal cortices, anterior and posterior cingulate cortices, posterior parietal cortex, and medial frontal cortex [17]. Patients complaining of problems with cognition often report that they are feeling confused, fuzzy or are falling asleep during conversations or reading activities. They may report forgetfulness, frequent accidents, slow reaction times and difficulties with problem solving, concentration and thinking [15]. In a comprehensive review by Moriarty *et al.* [18] the cognitive effects of pain is outlined, and particularly attention is a domain that is well studied. Chronic pain patients often report difficulties with attention, and several studies have demonstrated deficits in attention in different chronic pain conditions such as fibromyalgia, diabetic neuropathy, chronic low back pain and whiplash associated disorders. One explanation of attention problems in chronic pain patients may be that pain competes with other attention-demanding stimuli for limited cognitive reserves [19]. Legrain *et al.* [20] have proposed a neurocognitive model of attention and pain, which incorporate two modes of attention, a top-down and a bottom-up selection. The top-down-selection is an intentional and goal-directed process that prioritizes information relevant for current actions, and prefrontal and frontal areas of the brain are probably involved in these mechanisms. Bottom-up selections correspond to an unintentional stimulus-driven capture of attention by environmental events themselves. Beside problems with attention chronic pain patients also have problems with learning and memory. Compared to healthy controls chronic pain patients performed poorly on parameters including spatial and verbal working memory capacity, recognition working memory and long-term spatial memory [18]. More complex cognitive tasks as planning, organisation, control of conflicting thoughts, goal-directed behaviour, initiation of action and assessing the consequences of action have also been assessed in chronic pain patients, and the studies summarized by Moriarty *et al.* showed that these complex functions may be even more severely affected than less complex automatic processes. Although there seems to be sufficient evidence from the literature that pain is associated with cognitive impairment several confounders may complicate the picture. Especially psychological distress as anxiety and depression are emotional disorders that frequently accompany long-lasting pain and may have demonstrable adverse cognitive effects, most specifically on speed of mental processing and attentional functions. Anxiety effects involve slowed mental processing, blocked thoughts, and complaints of memory deficits [21]. Depression may lower cognitive performance in many aspects, but major cognitive dysfunction seems to appear specifically on tests of executive functions, processing speed, attention and memory [3-5]. Depression is often associated with cognitive impairment in several domains [22-26], which may persist even in the remitted stage [27]. Finally, motivation may be hampered during psychological distress and may influence neuropsychological testing considerably.

THE COGNITIVE EFFECTS OF OPIOIDS IN CHRONIC NON-CANCER PAIN

As a result of the increasing consumption of opioids in chronic non-cancer pain a number of “new” side-effects during long-term treatment have recently received attention. We have previously described opioid induced hyperalgesia, tolerance, addiction, hormonal and immunological deficiencies, and cognitive dysfunction [28]. Previous either narrative or systematic reviews have included controlled as well as uncontrolled studies of short and long-term opioid use making the interpretation of the outcomes difficult and decreasing the level of evidence. Five reviews concluded that more studies are necessary [1,29-32], three did not find any negative effect of opioid treatment [15,31,33] and one considered that each

patient has to be individually treated and assessed [34]. In an attempt to clarify the current evidence, our group did a systematic review only including controlled studies and summarizing and stratifying levels of evidence/recommendations [4]. For the purpose of the present review we updated the literature in March 2011 finding only one later study [35] added to the present review.

Thus, studies included were controlled designs, written in the English language and comprising patients with chronic non-cancer pain. The patients had received opioids for at least 1 month and were cognitively assessed solely by neuropsychological tests. Data was summarized and each study classified according to four aspects: 1) Study design (randomized controlled trials (RCTs) and outcomes research (non-randomized comparative studies (NCS) or observational studies (OS)) [36,37]; 2) Level of evidence (ratings from 1 to 5 and a to d, where 1a is the highest/best level [37]; 3) Grades of recommendation (ratings from A to D, where A is the highest/best supported by level 1 studies [37]; and 4) Quality of clinical trials (Jadad Scale: information given in each paper concerning randomization, double-blinding, withdrawals and drop-outs; scores from 0 to 5, higher scores mean better quality [38]).

Fourteen studies were included in the present review for analysis. Three studies were RCTs [39-41], two were NCS [42,43], and nine were OS classified as outcomes research [35,44-51]. The studies reported the following outcomes of long-term opioid treatment: Improvement, worsening and no effect of opioids on cognitive function (Table 1).

Improvements in the cognitive domains regarding information processing, attention, psychomotor speed, manual dexterity, and memory were observed in 2 RCTs [40,41] and in 2 NCS [42,43]. Attention/vigilance, working memory [47-49], psychomotor speed [44,48], sustained attention [48] and visual orientation [49] were deteriorated in patients on opioids compared to healthy controls in 5 OS. Higher plasma fentanyl level was associated with reduced attention, reaction time and vigilance [46], higher doses of oxycodone with reduced attention, vigilance and number of wrong answers in a reaction time test [49], and higher doses of transdermal buprenorphine with reduced vigilance [51].

The chronic pain condition itself may influence cognitive function bi-directionally and an association between pain relief and improved cognitive performance were found in 4 studies [44,47,48], while one found that a higher pain intensity was associated with improved working memory [48].

The three RCTs obtaining the highest quality scores [39,40,52] showed no cognitive alteration in the tests used or some improvement, but nevertheless they had limitations (lack of randomisation, blinding or control groups without opioids) that should impose cautious interpretation [39-41]. Only 2 longitudinal, randomised trials with blinding procedures have been published.

The outcomes of NCS [42,43] indicated no alteration or some improvement of cognitive functioning following opioid treatment. On the other hand, studies rated as lower level of evidence demonstrated no difference or worsening on cognitive function, when groups of chronic pain patients on opioids were compared with patients with neurological deficits [45], healthy controls [44,46,49,51], chronic pain patients without opioids [50] and different control groups consisting of chronic pain patients without opioids and healthy controls [47,48].

COGNITIVE FUNCTION AND CANCER PAIN

In patients with cancer cognitive dysfunction may be a persistent problem, from the time of diagnosis, during the trajectory of the disease, in palliative care and in cancer survivors. Studies have shown that diagnosing cancer produce psychological distress with memory related deficits even before chemotherapy was started [53,54]. In patients with advanced cancer, cognitive dysfunction are among the most frequently reported symptoms [55] and the preva-

Table 1. Summary of the Reviews

Characteristics	Reviews	
	Chronic non-cancer pain Kendall <i>et al.</i> 2010 ¹	Chronic cancer pain Kurita <i>et al.</i> 2009 ²
<i>Period of review</i>	Entire period available until Aug 2009	Entire period available until Nov 2007
<i>Databases</i>	PubMed, EMBASE, PsycInfo, CINAHL, Lilacs, and Cochrane Systematic Reviews	PubMed, EMBASE, PsycInfo, CINAHL, and Lilacs
<i>Inclusion criteria</i>	Patients with chronic non-cancer pain, at least 1 month of opioid treatment, controlled studies, cognitive assessment by neuropsychological tests, and English language	Patients with chronic cancer pain, in opioid treatment, controlled studies cognitive assessment by neuro-psychological tests, and English language
<i>Number of studies included in the original article</i>	13	10
<i>Number of studies included during update in Mar 2011</i>	1 (Nilsen <i>et al.</i> 2011) ³	1 (Kurita and Pimenta 2008) ⁴
<i>Studies quality</i>	14 - grade recommendation B	10 - grade recommendation B
<i>Number of studies that reported cognitive dysfunction</i>	4	8
<i>Number of studies that reported improvement/ better cognitive function when compared to controls</i>	5	1*
<i>Number of studies that reported no effect</i>	5	3
<i>Cognitive domains affected</i>	Memory Attention Visual orientation	Memory Attention Psychomotor speed Planning abilities
<i>Factors associated/correlated to cognitive dysfunction</i>	Higher morphine plasma concentration Higher pain intensity Comparison with healthy volunteers	Increasing the opioid dose Supplementary opioid dose Higher pain intensity Higher morphine plasma concentration Sedation Comparison with healthy volunteers
<i>Possible factors associated to better cognitive function</i>	Stable opioid treatment Long acting opioids	Long term treatment
<i>Main weak points in the studies</i>	Methodological limitations Sample sizes Healthy control groups Different opioids, different doses Different neuropsychological tests Lack of assessment before treatment	Methodological limitations Sample sizes Healthy control groups Different opioids, different doses Different neuropsychological tests Lack of assessment before treatment

*Same study presented worse and better cognitive functions when patients were compared to controls

¹ Reference [2]

² Reference [1]

³ Reference [30]

⁴ Reference [61]

lence ranges from 10% to 90% [56,57] with an increasing prevalence before death [58].

The clinical problem in the earlier stages of cancer disease is often the subtlety of the presentation of cognitive deficits. There may be a slight decrease in comprehension, loss of ability to think abstractly, difficulty in finding correct wording, slight forgetfulness, complaints of mental fatigue, difficulty in concentrating, and irritability. These problems are often unnoticed or may sometimes be attributed only to psychological distress [59]. The multi-system

impairment that accompanies progression of the cancer disease is undoubtedly associated with an increase in vulnerability towards cognitive dysfunction, which in later stages of the disease may be manifested as delirium [60].

Causes of the cognitive dysfunction in cancer patients may be broadly classified into three categories: disease related causes, treatment related causes and causes related to other factors [61-63]. The assessment of memory, thinking, judgement, attention and perception in cancer patients is influenced by a number of factors

within these categories, for example by the systemic disease which may directly affect cognition (e.g. brain metastases) or indirectly through metabolic disturbances (e.g. hypercalcemia), humoral mediators (e.g. cytokines), presence of emotional stress (e.g. anxiety and depression), physical symptoms (e.g. fatigue) or other factors unrelated to the disease (e.g. dementia or medication).

In cancer survivors chemotherapy was found to be associated with subtle and transient cognitive dysfunction detectable only with neuropsychological testing and affecting in particular memory, concentration and speed of information processing [64]. Cognitive complaints including problems related to memory, learning, language and concentration are frequently reported by breast cancer survivors, but it remains unclear whether this is more commonly found in breast cancer patients than in the general population. However, one study found lack of relationship between cognitive complaints and objective cognitive dysfunction measured by neuropsychological tests [65].

The Cognitive Effects of Opioids in Cancer Pain

Previous reviews on the cognitive effects of long-term opioid treatment in cancer patients have found that there were few studies available with a great diversity of designs and methods, and that confounding factors and limitations of those studies called for further high quality studies [9,15,30,60]. In an attempt to clarify this issue in more depth we have updated a systematic review on the cognitive effects of long-term opioid treatment in cancer patients, which was published in 2009 [3]. Terms related to cancer, opioid and cognition were used to build search strategies. The first search was performed in November 2007 and for the purpose of this review repeated in March 2011. The search in March 2011 revealed one new controlled study [66] which has been added to the present review. Studies included in the updated review were studies on patients with chronic cancer pain treated with long-term opioids and assessed by neuropsychological tests. The study design and level of evidence was classified as described above.

Eleven controlled studies (2 RCTs [67,68], 3 NCS [66,69,70], 5 cross-sectional [71-75], and 1 case-control [76]) were included in the review. Similarly to the studies with non-cancer patients with chronic pain, the studies reported: Improvement, worsening and no effects of opioids on cognitive function. The majority of studies (n=9) reported impaired cognitive function or no effect of opioids on cognition (Table 1).

The opioid treatment was shown to impair the cognitive performance in eight studies [69-71] [66,68,72-74]. The main functions affected were memory [68,69], working memory [66], attention [66], sustained attention [70-73] and planning abilities [66]. In three of the studies no differences were found [67,75,76]. In one study both cognitive deterioration (balance) and improvement (psychomotor speed) in patients treated with opioids were reported [74].

Significant correlations were observed between higher sedation scores and longer reaction times [71,73], between higher morphine plasma concentrations/metabolites and poor attention/structuring ability [74] and more severe pain and worse cognitive performance [66].

Considering the studies with higher level of evidence (RCTs), deficits in the cognitive function were associated to patients who underwent opioid dose increase [69] and patients who received supplemental doses of opioids [68]. This confirms the hypothesis that cognitive function can be sensitive to opioid dose increments, although tolerance to cognitive effects may develop after some time [30,69]. However, these studies had limitations related to designs/methods, characteristics and sample sizes that preclude definitive answers (Table 1).

Discussion

The widespread consumption of opioids in the population with chronic non-cancer pain has stimulated research in the cognitive

effects of long-term opioid treatment. However, the challenges in performing sound studies in this arena are manifold [44,46-49,51]. Areas of concern are the selection of control groups, concurrent medical or non-medical treatments, variations of pain intensity throughout the study and the influence of the total symptom burden over time.

Controlled designs with control groups are widely assumed to provide higher evidence than non-controlled designs. First of all, selecting the "right" control group for studies on cognitive dysfunction in chronic pain patients treated with opioids is a major challenge. The ideal control group should be chronic pain patients eligible for opioid therapy, but these patients are seldom used as control groups in long-term studies. Furthermore, patients without opioids chosen as controls may be quite different from those on opioids. Thus, the ideal design would probably be the RCT. However, double blind RCTs of opioid treatment may be very difficult to perform due to the prevalent side effect profiles, which would, unless the placebo closely mimics the side effects, disclose the study drug. But mimicking opioid side effects using an "active" placebo make comparison of cognitive effects difficult [77]. The selection of study patients is also hampered by the fact that treatment for chronic non-cancer pain frequently includes concurrent medications, which can affect cognitive function. In a study from our center, all patient subgroups performed worse than healthy controls, irrespective of drug classes or combinations of drug classes. Treatment with opioids was associated with impaired working memory [48]. Using healthy volunteers without chronic pain neglect the fact that chronic pain itself may impair cognition. This approach used in a number of studies [44,46,49,51] makes the cognitive effects of long-term opioid administration *per se* difficult to judge. As outlined above pain itself may have an arousal effect or may act as a mental stressor. By reducing the stressor (pain), cognitive balance may be re-established [44,78], and this phenomenon may be responsible for the cognitive improvement demonstrated in two of the RCTs [40,41].

When planning long-term studies on the chronic non-cancer pain population a number of confounders should also be taken in consideration, e.g. emotional distress, suffering, fatigue, anxiety, depression, and educational level. Most studies had major psychiatric/mental disorders as exclusion criteria. Only two studies investigated opioids, mood and cognition at the same time [42,44]: one study showed that depression was associated with poorer psychomotor speed [44] and the other that severe pain relieved by opioids improved mood [42]. Furthermore, longitudinal studies during "real" long-term opioid treatment should also consider the fact that both pain and co-morbidities, although "chronic" may change considerably in time [79].

Due to the limitations of current evidence regarding opioid effects on cognitive function in the chronic non-cancer pain population we need to consider different options. One option is to look at the available evidence, which over-all may indicate no or little deleterious effects of opioids on cognitive function. However, considering long-term administration of opioids as harmless implies risk taking and recent guidelines are clear in recommending caution with opioid prescribing and long-term monitoring [80]. Furthermore, the manifold other long-term consequences of opioid treatment e.g. opioid induced hyperalgesia, tolerance, addiction, hormonal and immunological deficiencies, which are emerging should also be taken into account [28]. Chronic pain patients and their families should be informed in detail about possible side effects and long-term consequences of opioid use including cognitive dysfunction. Finally, health care professionals should be alert to signs of cognitive dysfunction especially in patients, who are driving or working or have demanding leisure activities. A pause from work or activity relocation may be advisable during initial dose titration, dose changes, and other changes in the patient's condition.

Systematic assessment can be useful to monitor cognitive function over time and may guide adjustment of medications.

In the view of the complexity and variety of factors that can affect cognition in patients with pain and cancer, it is not surprising that there is a paucity of studies that selectively evaluates the cognitive effects of opioids in cancer populations. However, there has recently been an increasing focus on problems with cognitive dysfunction that can result from cancer and its treatments. The importance of unpacking aetiologies of cognitive dysfunction is obvious as reversibility makes some of them manageable. Detection of cognitive dysfunction in the early stages of the cancer disease process may have important implications for predicting more severe cognitive failure and even delirium in the later stages and may indeed have implications for interventions depending on aetiology (amphetamine derivatives, methylphenidate, modafinil, corticosteroids, hydration, erythropoietin, blood transfusion, etc). The Mini Mental State Examination (MMSE) is the most widely used instrument for screening cognitive impairment and it has been introduced as a popular assessment tool for cognitive impairment in cancer patients referred to palliative care [55]. Although, the MMSE has gained enormous popularity in palliative care, it is a long instrument and criticism has been raised towards this instrument regarding its lack of sensitivity and specificity [81]. There is limited information about the clinical validity of neuropsychological tests in chronic pain patients and apart from these clinical and research demands practical procedural requirements should also be considered. In the studies of the present review, cognitive domains investigated were primarily short-term memory, attention/vigilance and psychomotor speed. Digit Symbol Substitution [82], Trail Making [83], Stroop Task [84], Finger Tapping [85] and Continuous Reaction Time [86] were repeatedly used in most studies and enabled the researchers to detect even subtle cognitive changes. However, the clinical meaningfulness of these changes remains to be settled.

The choice of the control group for studies of the effects of opioids is equally important in the cancer population as in the chronic non-cancer pain patients, because healthy volunteers do not control for the cognitive effects of disease or treatment. As in the studies in the non-cancer population the educational level was most often not included and controlled for despite the fact that it may influence cognitive performance [87]. In many studies the assessment was performed in patients who were already on opioids (different types of opioids and different dose levels), which do not allow for measuring the cognitive state before treatment with opioids. Few studies had longitudinal sampling of data that raises questions about the effects attributable to progression of disease and the development of tolerance to the effects of opioids. As in non-cancer pain patients anxiety and/or depression are emotional disorders frequently observed in cancer patients. In the systematic review only two studies assessed mood [68,76]; however, no associations between mood and cognitive function were found.

There is a pronounced lack of information in relation to cognitive effects of opioids administered by other routes. In cancer patients, the step-wise clinical practice, World Health Organization ladder [88] may oppose the possibilities of randomisation between treatments. However, a solution to the problems of randomization in patients with a cancer disease that may be acceptable is to compare the parenteral route with the spinal route using continuous infusions. Since these two modalities are widely accepted as alternatives, randomised prospective crossover designs would be ethically possible, even though patients receiving these treatment options often are in late stages of cancer. Studies in opioid switching/rotation assessing cognition should also be feasible as well as on-demand use of short-acting opioids for breakthrough pain in cancer patients should be assessed in more depth. Only a small RCT (N=14) has assessed this wide spread treatment option in cancer patients with breakthrough pain [68].

Three studies were found that analysed associations between opioid dose, metabolite concentrations and cognitive performance, but only one study found associations between concentrations of morphine and its metabolites and cognitive deficits [74]. Other uncontrolled studies not included in the review [89] [90] also had divergent results regarding the cognitive effects of plasma concentrations of morphine metabolites. Significant correlations between high plasma morphine concentrations and poor scores for short-term memory and attention were observed in a study of 18 cancer patients assessed with five validated neuropsychological tests [89]. In contrast, a study with larger sample (n=298) did not demonstrate associations between morphine metabolites and cognitive function measured by the MMSE [90].

The specific nature and quality of the cognitive effects of opioids in cancer patients are still unclear. To improve research in this area, future studies must include experimental designs, randomised and controlled trials with cancer pain patients receiving opioids and cancer pain patients not receiving opioids, assessments before and after treatment, adequate sample sizes and neuropsychological tests, which have been specifically validated in cancer populations. Moreover, mechanisms by which opioids may affect cognition, opioid switching/rotation, supplemental short-acting opioids on-demand, individual differences/characteristics/genetics, emotional factors, other symptoms (fatigue, insomnia, among others), opioid interactions with other medications, need further research. Finally, future studies of cognitive effects of different types of opioids during long-term treatment are very desirable.

CONCLUSION

Two updated systematic reviews on the cognitive effects of long-term opioid treatment of chronic pain of non-malignant and malignant origin demonstrated in

- 1) Chronic non-cancer pain: The majority of the studies reported some improvement or no effect of opioids on cognition. Observing the three RCTs, that obtained the highest level of evidence, they also showed no and some improvement in cognition.
- 2) Cancer pain: The majority of studies reported impaired function or no effect of opioids on cognition. Considering the two RCTs with highest level of evidence, deficits in the cognitive function were associated with opioid dose increase and the use of supplemental doses of opioids.

Thus, cognitive function can be sensitive to opioid dose increments, although tolerance to cognitive effects may develop after some time.

CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

ACKNOWLEDGEMENT

None declared.

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