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Topical review

The cognitive effects of opioids in chronic non-cancer pain

Sally Elizabeth Kendall [a,b], Per Sjøgren [c,*], Cibele Andrucioli de Mattos Pimenta [d,e], Jette Højsted [a], Geana Paula Kurita [a,c,d,e]

[a] Multidisciplinary Pain Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[b] Cancer Pain Unit, Skåne Oncology Clinic, Lund University and Lund University Hospital, Lund, Sweden
[c] Section of Acute Pain Management and Palliative Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[d] School of Nursing, University of Sao Paulo, Sao Paulo, Brazil
[e] The State of Sao Paulo Research Foundation, Sao Paulo, Brazil

1. Introduction

In the last decade a rapidly increasing use of opioids for chronic non-cancer pain has been reported from several countries [37]. Concerns regarding opioid treatment of chronic non-cancer pain have primarily been based on the fear of addiction and diversion [36,37]. However, other potentially important clinical issues such as physical dependency, tolerance development, cognitive dysfunction, abnormal pain sensitivity and dysfunction of the immune and reproductive systems may give rise to concerns [14].

One of the major worries of initiating long-term, sometimes life-long, opioid treatment in patients with chronic non-cancer pain is the potential introduction of cognitive dysfunction, manifested as e.g. impaired capacity for concentration, deficits in information processing and memory, slower psychomotor speed and reaction time. Previous reviews on opioids and cognition [3,4,8,18,19,34,39,40] have attempted to find a relationship between long-term opioid use and cognitive function in chronic non-cancer pain patients in order to establish recommendations. Five reviews [3,18,19,39,40] concluded that the evidence needed to be supplemented. Three reviews observed no deleterious effect of continuous opioid use on cognition [4,8,18], and one concluded that guidelines on opioid effects on cognition should be addressed on a patient-specific basis [34]. All reviews included controlled and uncontrolled studies as well as short- and long-term opioid use, and only one included a grading of the evidence [19].

The ongoing discussion on cognitive effects of long-term opioids in chronic non-cancer pain justifies a new attempt to systematically review and grade current evidence, with the aim of supplementing current recommendations.

2. Methods

The research question "Does the long-term use of *opioids* interfere with the cognitive function in patients with chronic non-cancer pain?" guided the literature search. Terms related to pain, opioid and cognition were used to build search strategies. The search was performed on July/August 2009 and included the entire period available in PubMed, EMBASE, PsycInfo, CINAHL and Lilacs. Cochrane Systematic Reviews were also searched. Eligibility criteria for article selection were patients with chronic non-cancer pain, at least 1 month of opioid treatment, controlled study, cognitive assessment by neuropsychological tests and written in English language. Studies using self-report cognitive assessment or health professional opinion were excluded. We hand searched reference lists from review articles.

Data were summarized and each study classified according to four methods is described below:

- *Study design:* randomized controlled trials and outcomes research (non-randomized comparative studies or observational studies) [9,25].
- *Level of evidence:* ratings from 1 to 5 and a to d, where 1a is the highest/best level [25].
- *Grades of recommendation:* ratings from A to D, where A is the highest/best supported by level 1 studies [25].
- *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 [15].

3. Results

We selected 30 articles from the databases. Sixteen were excluded as duplicates and one was excluded because the study analyzed the analgesic effects of opioids compared to an "active placebo" (benztropine), which mimics the opioid effects on cognitive function [23]. No studies were included by hand search. The 13 remaining studies were analyzed (Table 1). Three studies were randomized controlled trials (RCTs) [16,26,29], two were non-randomized comparative studies (NCSs) [13,35], and eight were observational studies classified as outcomes research [2,5,11,12,30–32,38].

All studies had similar exclusion criteria. Educational level was not controlled for in most studies and concomitant medications were mentioned in six studies [2,13,16,32,35,38].

In two RCTs [16,29] and in two NCSs [13,35] improvements in information processing, attention, psychomotor speed, manual

* Corresponding author. Address: Section of Acute Pain Management and Palliative Medicine, Rigshospitalet, Blegdamsvej 9, Afsnit 4114, 2100 Copenhagen, Denmark. Tel.: +45 3545 7384; fax: +45 3545 7349.
E-mail addresses: p.sjogren@mail.dk, rh12244@rh.regionh.dk (P. Sjøgren).

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Table 1
Summary of studies.

Study	Design	Sample (mean age or range – years)	Opioid type and daily dose	Assessment schedule	Level of evidence/ grade of recommendation/ Jadad Scale score	Tests and outcomes		Correlation: cognitive function and opioid	Correlation: cognitive function and pain
1. Raja et al. [26]	Randomized controlled trial (double-blind, crossover)	76 patients postherpetic neuralgia (71.0)	Morphine 91 mg/d, methadone 15 mg/d	Baseline/after 6 weeks	2b/B/5	Symbol Substitution (attention/ psychomotor function)	No difference	–	–
						The Hopkins Verbal Learning (verbal learning)	No difference		
						Grooved Pegboard (manual dexterity/psychomotor speed)	No difference		
2. Rowbotham et al. [29]	Randomized controlled trial (double-blind)	43 patients high-strength capsules of levorphanol (65.0) 38 patients low-strength capsules of levorphanol (64.0)	Levorphanol mean high doses = 9 mg/d and mean low = 3 mg/d	Baseline/after 8 weeks	2b/B/4	Symbol Digit (attention/ immediate recall)	Improvement *Both groups*	–	–
3. Jamison et al. [16]	Randomized controlled trial (crossover)	144 patients low back pain (46.3)	Oxycodone mean 33 mg/d, fentanyl mean 43 μg/h	Baseline/after 90 and 180 d	2b/B/2	Digit Symbol (attention/ psychomotor function)	Improvement	No	No (statistical test only at baseline)
						Trail Making B (visual information processing/ motor speed/attention)	Improvement *Both groups*		
4. Tassain et al. [35]	Non-randomized comparative study	18 patients on morphine (46.0)	Morphine SR 40–140 mg/d	Baseline/after 3, 6, 12 months	2c/B	Free and Cued Delayed Selective Reminding Test (immediate recall)	No difference	No	Lower pain – better attention (Stroop)
		10 patients who stopped morphine due to poor pain relief/side-effects (51.4)				Stroop Task (attention)	Improvement		
						Trail Making (visual (information processing/ motor speed/attention)	No difference		
						Digit Span (sustained attention/short-term memory)	No difference		
						Verbal Fluency (sustained attention/semantic memory)	No difference		
						Digit Symbol (visual (information processing/motor speed/attention)	No difference		
5. Haythornthwaite et al. [13]	Non-randomized comparative study	19 patients on long-acting opioids (50.8) 10 patients on short-acting opioids (52.2)	Methadone or morphine SR 111.1 mg/d 19.0 mg/d	Baseline/after 3–5.8 months	2c/B	Grooved Pegboard (manual dexterity/psychomotor speed)	No difference	–	–
						Hopkins Verbal Learning (memory)	No difference		
						Trail Making Test (visual (information processing/motor speed/attention)	No difference		
						Digit Symbol (visual information processing/motor speed/ attention)	Improvement		
						Digit Span (immediate attention/ concentration/verbal information processing)	No difference		

6. Galski et al. [12]	Outcomes research (observational cross-sectional)	16 patients pain (48.4) 327 cerebrally compromised patients from historical control group (46.0)	Morphine SR, transdermal fentanyl, short-acting opioid as rescue ⩾30 mg oral morphine	After 6 months opioid treatment	2c/B	Digit Symbol (visual (information processing/motor speed/attention) Trail Making A (visual (information processing/motor speed/attention) Double Letter Cancellation (visual information processing/motor speed/attention) Visual Form Recognition (visuospatial perception, visuopraxis, visual memory) Rey–Osterreith Complex Figure (visuospatial perception, visuopraxis, visual memory) Ravens Progressive Matrices (planning–problem solving)) Porteus Maze (planning–problem solving)	No impairment Patients on opioids outperformed cerebrally compromised patients in all tests	–	No
7. Sabatowski et al. [30]	Outcomes research (observational cross-sectional)	30 patients low back neuropathic or miscellaneous pain diagnosis (50.0) 90 healthy (53.0)	Transdermal fentanyl 25–400 μg/h	After 30–1530 d opioid treatment	2c/B	Attention test Reaction time under pressure Visual orientation Motor coordination Vigilance test	No difference No difference No difference No difference No difference	Plasma level and reaction time ($r = 0.48$, $p = 0.04$), number of errors ($r = 0.673$, $p = 0.002$) and vigilance ($r = 0.573$, $p = 0.01$)	No
8. Won et al. [38]	Outcomes research (observational longitudinal retrospective)	120 patients on long-acting opioids (81.0) 693 patients on short-acting opioid (83.9) 1389 on at least one standing order for short acting analgesics (83.0) 1467 no opioid (83.6)	Long- and short-acting opioids	>6 months	2c/B	Cognitive Performance Scale (general mental status)	No difference	–	–
9. Dagtekin et al. [5]	Outcomes research (observational cross-sectional)	30 patients with low back, neuropathic or miscellaneous pain (53.0) 90 healthy (53.0)	Transdermal buprenorphine 45 μg/h	After at least 4 weeks, stable treatment for 12 d	2c/B	Attention test Reaction time under pressure (attention) Visual orientation/tachistoscopic perception Motor coordination Vigilance test	No difference No difference No difference No difference No difference	Higher dose and number of wrong answers on vigilance test ($r = 0.48$, $p = 0.027$)	No
10. Sjøgren et al. [32]	Outcomes research (observational cross-sectional)	40 patients (46–74) 40 healthy (49–78)	Morphine SR, methadone, ketobemidone, buprenorphine, tramadol 15–300 mg/d	After 14 d stable dose	2c/B	Continuous Reaction Time (sustained attention) Finger Tapping (psychomotor speed) Paced Auditory Serial Addition (working memory)	Worse Worse Worse	No	Higher pain scores – better working memory ($p = 0.025$, $p = 0.017$, Paced)

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Sample (mean age or range – years)	Opioid type and daily dose	Assessment schedule	Level of evidence/ grade of recommendation/ Jadad Scale score	Tests and outcomes		Correlation: cognitive function and opioid	Correlation: cognitive function and pain
11. Sjøgren et al. [31]	Outcomes research (observational cross-sectional)	21 patients no medication (40.4) 19 patients long-term oral opioids (46.4) 18 patients antidepressants/ anticonvulsants (40.3) 33 patients long-term opioids, antidepressants, anticonvulsants (48.1) 64 healthy (47.6)	Metadone, morphine, oxycodone, tramadol, buprenorphine, fentanyl 4–450 mg/d	After 21 d of stable opioid treatment	2c/B	Continuous Reaction Time (sustained attention) Finger tapping (psychomotor speed) Paced Auditory Serial Addition Task (working memory) Mini-mental State Examination (general mental status)	Worse Worse Worse Worse[a]	No	Higher pain scores – worse information process, working memory, attention ($p = 0.0023$, Paced)
12. Byas-Smith et al. [2]	Outcomes research (observational cross-sectional)	21 patients on opioids (47.7) 11 patients no opioids (46.5) 50 healthy (42.6)	Hydromorphine, methadone, morphine, hydrocodone, oxycodone, tramadol, codeine 118 mg/d (morphine equivalent dose)	After at least 1 week stable dose	2c/B	Obstacle course (driving) Test of variables of attention Digit Symbol Substitution (visual information processing/motor speed/attention)	No difference No difference Worse	–	Lower pain scores – better attention ($p < 0.01$, Digit Symbol)
13. Gaertner et al. [11]	Outcomes research (observational cross-sectional)	30 patients on oxycodone SR (55.0) 90 healthy (55.0)	Oxycodone SR 76 mg/d	After at least 4 weeks, stable treatment for 12 d	2c/B	Attention test Reaction time under pressure (attention) Visual orientation/tachistoscopic perception Motor coordination Vigilance test	No difference Worse No difference No difference No difference	Reaction time under pressure ($r = 0.45$, $p = 0.01$), vigilance test ($r = -0.41$, $p \leqslant 0.05$), attention ($r = 0.38$, $p = 0.038$)	No

SR = sustained release.

[a] Opioid combined with tricyclic antidepressant and/or anticonvulsant.

dexterity, and memory were observed following opioid treatment. In four outcome research studies patients on opioids had worse attention, vigilance, working memory [2,11,31], psychomotor speed [31,32] and sustained attention [31] when compared to healthy controls.

Higher plasma fentanyl level was associated with worse attention, reaction time and vigilance [30], higher doses of oxycodone with poor attention, reduced vigilance and wrong answers in a reaction time test [11], and higher doses of transdermal buprenorphine with reduced vigilance [5].

Three studies found significant correlations between improved cognitive performance and pain relief [2,31,32] and one study showed higher pain intensity correlated with improved working memory [31].

One of the three RCTs obtained maximum score according to the Jadad Scale [26]. Lack of information about randomization and/or no blinding were weaker points in the two other RCTs [16,29]. In addition, lack of control groups without opioids was an important limitation in two RCTs [16,29]. Three studies had level of evidence 2b [16,26,29], indicating moderate grade of recommendation (B). Other studies had level of evidence 2c, also indicating moderate grade of recommendation (B). Studies rated as higher design quality showed either no effect of opioids on cognitive functioning [26] or some improvement [16,29].

4. Discussion

This review differs from previous reviews by excluding non-controlled and experimental studies, opioid treatment for less than a week, and by quality rating studies. On the basis of high quality evidence pertaining to long-term opioid treatment and cognition, current evidence for benefit, harm or lack of appreciable effect of a long-term stable opioid treatment on cognitive functioning in non-cancer pain patients is still limited. Despite the fact that studies of best quality-RCTs [16,26,29] showed no alteration or some cognitive improvement, they had limitations that impose cautious interpretation. Similarly, the results of the NCSs [13,35] indicated no alteration or some improvement of cognitive functioning following opioid treatment. On the other hand, studies of 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 [12], healthy people [5,11,30,32], chronic pain patients without opioids [38] and different control groups consisting of chronic pain patients without opioids and healthy people [2,31].

Six studies of the present systematic review had cross-sectional designs, which can establish associations [2,5,11,30–32], but not causality. We found only two longitudinal, randomized trials with blinding procedures [26,29]. Long-term double blind, randomized controlled trials may not be possible unless the placebo closely mimics the side effects of opioids, which in turn may cause problems in assessing cognitive functioning [23]. Longitudinal studies during "real" long-term opioid treatment should also consider the fact that pain and co-morbidities, although "chronic", change in time [7].

The control populations of studies differed considerably. Using patients with neurological disorders or patients who had failed in opioid treatment, also makes the results' applicability to clinical practice difficult [12,35]. Other studies used healthy volunteers without chronic pain and co-morbidities as controls. However, the "ideal" control group is very difficult to determine, as chronic pain patients without opioids may be different from those on opioids. Treatment for chronic non-cancer pain frequently includes concurrent medications, which can affect cognitive function. In a study from our centre, all patient sub-groups performed worse than healthy controls, irrespective of drug classes or combinations of drug classes [31].

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 [21,32]. The latter phenomenon may be responsible for the cognitive improvement demonstrated in two of the RCTs [16,29]. However, the effects of pain on cognitive functioning may not be related in a simple fashion to its immediate sensory-discriminative features (e.g. pain intensity), and concomitants of chronic pain (e.g. emotional distress, suffering and fatigue) may be important mediating variables. Most studies had major psychiatric/mental disorders as exclusion criteria, because depression is highly prevalent in chronic non-cancer pain and associations between depression and cognitive complaints have been shown [28]. Only two studies investigated opioids, mood and cognition at the same time [13,32]: one showed that depression was associated with poorer psychomotor speed [32] and the other showed that severe pain relieved by opioids improved mood [13].

The goals of chronic pain therapy are to reduce pain intensity, improve quality of life and mental and physical functioning. Due to the limitations of current evidence regarding opioid effects on cognitive function we as clinicians are facing a crossroad. The first option is to regard the available evidence, which shows no deleterious effects of opioids on cognitive function; however, according to strict grading/classification of study quality there are a number of methodological flaws. Consequently considering long-term administration of opioids as harmless implies risk taking. The second option is to take studies of lower level evidence with several methodological limitations into account and be careful with opioid prescribing, which is recommended for several reasons [37].

A reasonable advice would be to inform patients and their families about possible side effects and long-term consequences of opioid use including cognitive dysfunction. We already know from the literature that cognitive complaints in chronic non-cancer patients are highly prevalent [22]. Furthermore, other factors like individual patient characteristics such as advanced age, pain and co-morbidities, initial opioid prescribing in opioid naïve individuals, titrating to stable doses, dose changes during stable long-term treatment and higher opioid doses may contribute to cognitive dysfunction [1–3,16,19,20,31,32,35]. Thus, 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.

Furthermore, systematic assessment can be useful to monitor cognitive function over time and may guide adjustment of medications. There exist numerous neuropsychological tests, however, there is limited information about the clinical validity of these tests in chronic pain patients. Ideally an assessment tool or a test battery should fulfil criteria of reliability, validity and norm standardization, but apart from these clinical and research demands practical procedural requirements should also be considered. First of all, the test(s) should be of short duration and easy to administer, and secondly the test(s) should be suitable for the patient's situation. Despite all the criticism regarding the low sensitivity for mild cognitive alterations, the Mini-mental State Examination [10,31] is probably still the most used and translated tool to assess mental function. It is a quite easy test to administer and provides a broad overview of cognitive functions, but it is originally designed for demented individuals and may be too rough for detecting more subtle changes of cognitive functioning [10,31]. The cognitive domains analyzed in the studies of the present review were primarily short-term memory, attention/vigilance and psychomotor speed. Therefore, a preference to explore and assess these cognitive domains seems to be obvious. Digit Symbol Substitution [33], Trail Making [27], Stroop Task [17], Finger Tapping [24] and Continuous Reaction

Time [6] were repeatedly used in most studies and enabled the researchers to detect even subtle cognitive deficits. However, the clinical meaningfulness of these changes remains to be settled.

5. Future directions

In order to analyze the effects of opioids on cognition we need to improve study design and carry out studies in this specific patient population to confirm validity and reliability of clinically relevant neuropsychological tests. Future validation studies should include establishment of cut off points based on specificity and sensitivity, so that patients with clinical relevant cognitive dysfunction could be separated from those without. Based on improved assessment tools the cognitive effects of different types of opioids, dose levels and changes may be more precisely measured and compared.

Apparently, the current concern about the cognitive effects of opioids in chronic non-cancer pain patients is limited. The Clinical Trials website of US National Institutes of Health had until October 2009 more than 1300 patients included in registered opioid trials, however, none of them included assessments of cognitive functions. Thus, there are no studies currently considering risk evaluation mitigation strategies (REMs) related to cognitive dysfunction.

Based on the rapidly increasing opioid consumption in chronic non-cancer pain in western countries and the incipient research activities regarding the cognitive effects of long-term opioids, it seems timely to have international collaboratives to propose and organise focussed research activities in the field. Only then we will have strong evidence on which to base recommendations to patients, employers and insurers.

Conflict of interest

The authors declare no conflict of interest.

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