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REVIEW ARTICLE

The cognitive effects of opioids in cancer: a systematic review

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Abstract
Objective and methods In order to better understand the effects of opioids on the cognitive function in cancer pain patients, a literature search was performed in PubMed, EMBASE, PsycInfo, CINAHL and Lilacs databases. Ten controlled trials were selected and classified according to the study design, the level of evidence, and opioid regimen.
Result Six studies reported association between poor cognitive performance (reaction time, attention, balance, and memory) and opioid use.
Conclusion These cognitive deficits were captured with neuropsychological tests; however, their clinical relevance is still uncertain.

Keywords Cancer pain · Cognition · Opioids · Neuropsychological assessment · Palliative care

Introduction

In patients with advanced cancer, cognitive disorders are among the most frequent symptoms, and its prevalence ranges from 10% to 90% [14, 45, 46, 49], with an increasing prevalence before death [36]. Those cognitive disorders may be ascribed to a variety of causes, which according to etiology can be classified in three main categories: disease related causes, treatment related causes, and causes related to other factors [28, 31, 41]. Obviously, the assessment of memory, thinking, judgment, attention, and perception in cancer patients is influenced by a number of factors within these categories, for example, by the very nature of the systemic disease which, in turn, may directly affect cognition (e.g., brain metastases), or more indirectly through metabolic disturbances (e.g., hypercalcemia), humoral mediators (e.g., cytokines), presence of emotional distress (e.g., anxiety and depression), physical symptoms (e.g., fatigue); other factors unrelated to cancer (e.g., dementia); and medications (e.g., opioids).

Opioids are highly recommended by the World Health Organization [53] and the analgesic effect is widely recognized in cancer pain control. In addition, they are commonly prescribed in any phase of the cancer disease, when pain is reported, and represent an asset to pain management due to no ceiling dose. As a result of the widespread opioid use and improvement of anti-cancer therapies, there is a growing interest in studying the cognitive effects of long-term opioid treatment in cancer patients. The clinical problem in the earlier stages of cancer disease is often the subtle presentation of impaired cognition. There may be a slight decrease in comprehension, loss of ability to think abstractly, difficulty to find the correct wording, slight forgetfulness, complaints of mental fatigue, difficulty in concentrating, and irritability. The multi-system impairment that accompanies progression of the cancer disease is probably associated with an increase in vulnerability toward cognitive impairment, which in the late stages of the disease may be manifested as delirium [27].

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Disease-related and pharmacologically induced cognitive dysfunctions are extremely difficult to separate clinically as well as scientifically. The concept of "symptom clusters" refers to the concomitance of symptoms, which are related to each other in a logical or predictable way, could be in play regarding cognition [6, 7, 15]. For instance pain, fatigue, sedation, and depression may simultaneously influence cognitive function. In addition, the anticancer treatment as well as supportive and palliative treatments may also have cognitive effects.

Cancer patients complaints of cognitive deficits have not yet been directly associated with objective measures of cognitive function [24]. However, the precision and sensitivity of neuropsychological measurement techniques make them valuable instruments for investigating even small and subtle behavioral alterations. It is noteworthy that most neuropsychological assessment in cancer pain is engaged in domains of attentional capacity, psychomotor speed, information processing speed, and short-term memory [4, 5, 9, 11, 12, 23, 33, 42–44, 47]. However, no consensus is yet established concerning neuropsychological assessment of cognition in cancer pain patients.

In order to better understand the role of the opioids in this intricate issue, this systematic review solely focused on literature in which the specific aim was to study cognitive effects of opioids in cancer patients by using neuropsychological measurement techniques in controlled studies.

Methods: literature-search strategy

The literature search was based on conceptual strategy PICO, an acronym for patient, intervention, comparison, and outcome, which are essential elements for providing a framework [40]. Adequate controlled terms (medical subject headings or subject descriptors, which are used for the indexation of articles in the databases) and not controlled terms (textual words and their synonyms related to cancer, opioids, and cognition) were used to elaborate two search strategies, which fitted the characteristics of different databases (Table 1). Moreover, "search limits," tools available in the database programs, were used in some searches. In this case, the strategy was limited to controlled clinical trials, humans, and English language. The search was performed in November 2007 and included PubMed, EMBASE, PsycInfo, CINAHL, and Lilacs. The inclusion criteria were patients with chronic cancer pain, in opioid treatment, assessment by neuropsychological tests, and controlled studies (patients and healthy people could compose control groups or the patients could be their own controls). In addition, a hand search in personal files was also done.

All abstracts were read and the selected full articles were analyzed according to the opioid regimen of treatment and

Table 1 Search strategies and distribution of the results

Descriptors	PubMed 1950–2007 *n*	EMBASE 1980–2007 *n*	CINAHL 1982–2007 *n*	PsycInfo 1806–2007 *n*	LILACS 1982–2007 *n*	Total *n*
Cancer OR cancer/neoplasm OR tumor OR tumor/cancer AND opioid OR opioids AND cognition OR cognitive OR cognition/drug effects OR cognition/function OR cognition abilities OR cognition assessment OR cognition deficits OR cognition difficulties OR cognition disorders OR cognition disorders/drug therapy OR cognition dysfunction OR cognitive function OR cognitive deficits OR cognitive impairment OR psychomotor performance OR speed OR attention OR attentional capacity OR reaction time OR memory OR information processing OR driving OR neuropsychological assessment	444	0	0	0	0	444
Cancer OR neoplasm OR tumor AND opioid OR opioids AND cognition OR cognitive OR drug effects OR function OR cognition abilities OR cognition assessment OR cognition deficits OR cognition difficulties OR cognition disorders OR cognition dysfunction OR cognitive function OR cognitive deficits OR cognitive impairment OR psychomotor performance OR speed OR attention OR attentional capacity OR reaction time OR memory OR information processing OR driving Or neuropsychological assessment	0	123	21	11	0	155
Duplicate	–	4	1	4	0	9
Total	444	119	20	7	0	590
Selected	1	5	0	0	0	6

divided in three main categories: oral opioids, opioids administered by alternative routes, and/or opioid rotation and morphine metabolism. The study design was classified according to Fletcher, Fletcher and Wagner [19] and in levels of evidence from 1 to 5 and grades of recommendation from A to D, according to Oxford Centre for Evidence-based Medicine [38], which reflects evidence consistency in decreasing order. Main validated neuropsychological tests used in cancer patients are given in italics and a short procedural description can be found in the Table 2. Differences in methods, design, neuropsychological tests, and patient populations precluded any attempt of meta-analysis. An overview about the findings is presented in the following.

Results

The search resulted in 590 abstracts, from which six were selected. In addition, four studies found by hand search were also included (Table 1). A total of ten controlled studies (two randomized clinical trials, two non-randomized clinical trials, five cross-sectional, and one case-control), were published between 1989 and 2005 (Table 3). Six studies reported association between worse cognitive performance and opioid treatment, three reported no differences, and one demonstrated both cognitive deterioration and improvement in patients treated with opioids (Table 4). Correlation analyses were done in six studies (Table 5); significant correlations were observed between higher sedation scores and longer reaction times [4, 43] and between higher morphine plasma concentrations/metabolites and poor attention/structuring ability [47]. Regarding to the analysis of evidence, four studies were level 2b, five were 2c, and one was level 4; the majority had grade of recommendation B (Table 6). Considering the studies with higher level of evidence, deficits in the cognitive function were associated to patients who underwent opioid dose increase [9], received supplemental doses of opioids [23], and were compared to healthy controls [42].

Oral opioids

In the controlled studies on oral opioids, exclusion criteria were the presence of dementia and/or encephalopathy, a history of drug and/or ethanol abuse, renal and hepatic

Table 2 Description of the main neuropsychological tests cited in the studies

Test	Description
Continuous reaction time [16]	Computerized test to measure sustained attention or vigilance, i.e., the ability of the individual to attend to and respond rapidly to external stimuli for an extended period of time. Through headphones, auditory signals (500 Hz, 90 dB) are delivered to the patient at random intervals (2–5 s) over a period of 10 min. The patients are instructed to press a button as soon as they heard the sound, using the first finger of the dominant hand. A computer registered the time from emission of the sound signal to activation of the button. Reactions times are measured in 1/100 s.
Finger tapping test [37]	A relatively pure measure of psychomotor speed. In addition of being sensitive to lesions of motor structures of the cerebral hemispheres, detecting lateralized disability, psychomotor slowing is considered a non-specific consequence of cerebral dysfunction. The test requires the patient to tap a key as fast as possible. The key is attached to a device for recording the number of taps. The second finger of each hand make five 10-sec trials with brief resting periods between the trials.
Paced auditory serial addition task [20]	A sensitive and complex measure of attention, concentration, working memory, and speed of information processing. The test requires addition of simple digits presented from a tape recorder or a computer in four series of a successively higher pace of presentation. The task, which also reflects the capacity for divided attention, is sensitive to minor attention deficits
Prose recall [51]	Subtests from Rivermead Behavioural Memory Test (RBMT) assess immediate and delayed episodic memory. The RBMT was specifically designed to test performance on everyday memory tasks. The subjects listen to prose passages (short story) and are asked to recall them immediately and after sometime (delayed recall)
Stroop task [22]	A test of attention and susceptibility to interference. In the first two tasks, the subject must read as far as possible 100 color words in red, blue and green printed in black and white (reading score) or 100 colored dots in red, blue and green (color naming score). The last task is an interference condition in which the color to be named is spelled in an incongruent color name (e.g. the word "red" is written in blue). The task is to name the color of the letters (e.g., green) and to inhibit the strong tendency to read the word spelled (interference score).
Trail-making Test Form A and B [39]	The A form is a timed, connect-the-dots task that requires sustained attention and psychomotor speed. The B form is a test of visual information processing involving psychomotor speed and attention. The subject is instructed to draw lines to connect consecutively numbered and lettered circles by alternating between the two sequences. The subject is urged to connect the circles as fast as possible without lifting the pencil from the paper. Scoring is based on the number of seconds needed to successfully complete the test.

Table 3 Description and classification of the studies according to design

Database	Study	Design	Control group	Follow-up	Data collecting schedule*	Intervention
1. Hand search	Bruera et al. 1989 [9]	Controlled clinical trial	Yes	2 days	Before scheduled dose and after 45 min, results are the average of 2 days	Increasing opioid dose
2. Hand search	Sjøgren et al. 1989 [42]	Controlled clinical trial	Yes	No	Before catheter insertion and 1–2 weeks after epidural stable doses. Last dose 45–375 min before assessment	Epidural opioids
3. EMBASE	Banning et al. 1990 [4]	Cross-sectional	Yes	No	Patients already in opioid treatment	No
4. EMBASE	Banning et al. 1992 [5]	Cross-sectional	Yes	No	Patients already in opioid treatment for 40–120 days	No
5. EMBASE	Sjøgren et al. 1994 [43]	Cross-sectional	Yes	No	Patients already in opioid treatment	No
6. EMBASE	Vainio et al. 1995 [47]	Cross-sectional	Yes	No	Patients already in opioid treatment (mean=96 days) 90 min after last dose	No
7. Hand search	Clemons et al. 1996 [12]	Case-control	Yes	22 days	Patients already in opioid treatment (five to six assessments) 90 min after oral morphine solution dose and 4 h after controlled-release morphine	No
8. PubMed	Christrup et al.1999 [11]	Randomized controlled clinical trial (cross-over, double-blind, double-dummy)	Yes	12 h	Before and after opioid dose (1, 2, 4, 6, 10, 12 h)	Immediate release and controlled release morphine tablets
9. EMBASE	Sjøgren et al. 2000 [44]	Cross-sectional	Yes	No	Patients already in opioid treatment (2 weeks of stable treatment)	No
10. Hand search	Kamboj et al. 2005 [23]	Randomized controlled clinical trial (cross-over, double-blinded, placebo controlled)	Yes	No	Immediate recall before and after opioid dose, but majority of tests 45 min after dose, 2 days of interval between phases	Immediate release morphine

*Assessment before and or after opioid treatment.

impairment, metabolic disturbances, ongoing or recent anticancer therapy, acute progression of disease, brain metastases, a history of head injury or other neurological and/or physical dysfunctions that could interfere with the tests. In addition, four studies considered the use of psychotropic drugs other than opioids as an exclusion criterion [4, 5, 43, 47]. The cognitive effects of oral opioids are of major interest in the following clinical situations: (1) stable long-term treatment, (2) increase of the daily dose, and (3) use of supplemental short-acting opioids on top of regular daily doses (Tables 4 and 5).

Stable long-term treatment

In order to study the cognitive influence of long-term oral opioids, a cross-sectional study measuring *continuous reaction times* (CRT) compared 34 cancer patients treated with stable doses of morphine (30–920 mg/day) with 32 healthy controls taking no opioids [4]. Age and education level were not controlled for between-groups. Measurement of sedation, pain, and time from last medication was registered. Opioid-treated cancer patients performed statistically significantly poorer on CRT compared to the control group.

Another cross-sectional study measuring CRT in cancer patients receiving non-opioid analgesics either alone (n=16) or in combination with oral opioids (n=16) was performed by the same research group [5]. Patients from each group were matched regarding age and Karnofsky Performance Status (KPS). There was no information about educational level. At the time of evaluation the opioid treated group had received stable and pure daily doses of morphine or equianalgesic doses of other pure agonists for >2 weeks. In the opioid group, statistically significant prolongations of CRT as well as higher sedation scores were demonstrated.

Using a similar cross-sectional study, Vainio et al. [47] investigated the effects of oral morphine administration using a computerized test for driving ability originally designed for professional motor vehicle drivers and a number of other tests including neuropsychological measures (*finger tapping test* [FTT], reaction times, posture control, and thermal discrimination). A group of 24 cancer patients on sustained release morphine was compared with 25 cancer patients with no pain and no regular intake of analgesics. There were no differences between the two groups regarding age, sex, educational background, duration of illness, performance status, psychological state, and intelligence. The results showed that in the morphine group balancing with closed eyes was significantly poorer; however, finger tapping with the preferred hand was faster. The latter could have been interpreted as psychomotor speed was faster as a result of morphine treatment. These

Table 4 Studies on the cognitive effects of opioids in patients with cancer pain

Study	Design	Comparison (*n*)	Differences in age /education between groups	Cognitive functions assessed	Tests	Result opioid-association
1. Bruera et al. [9]	Controlled clinical trial	20 patients in opioid stable dose for 7 days or more 20 who had dose increasing at least 30% less than 3 days before study admission	nc/nc	Psychomotor speed, memory, calculation	Finger tapping, arithmetics, reverse memory of digits, visual memory	Worsening in all functions
2. Sjøgren et al. [42]	Controlled clinical trial	14 patients in oral opioid and subsequent stable epidural opioid therapy 20 healthy	no/nc	Sustained attention and vigilance	Continuous reaction time	Worse sustained attention
3. Banning et al. [4]	Cross-sectional	34 patients treated with stable doses of opioid 32 healthy volunteers	nc/nc	Sustained attention and vigilance	Continuous reaction time	Worse sustained attention
4. Banning et al. [5]	Cross-sectional	16 patients with opioids 16 patients without opioids	no/nc	Sustained attention and vigilance	Continuous reaction time	Impaired sustained attention
5. Sjøgren et al. [43]	Cross-sectional	8 patients oral morphine 8 epidural morphine 8 intramuscular morphine 44 healthy volunteers	no/nc	Sustained attention and vigilance	Continuous reaction time	Worse sustained attention
6. Vainio et al. [47]	Cross-sectional	24 patients with pain and opioids 25 without pain nor opioids	no/no	Driving ability, psychomotor speed, posture control, attention, reaction time	Reaction time (auditory, visual, associative stimuli), finger tapping, force platform, Middlesex method, ART-90	Worse balance, better psychomotor speed
7. Clemons et al. [12]	Case-control	7 patients in opioids treatment 6 patients without opioids 16 healthy	nc/nc	Reasoning ability, language, concentration, vigilance, psychomotor speed, memory	Adult reading test, logical memory test, grammatical reasoning test, reaction time, Stroop color-word test, mood adjective checklist (University of Wales)	No differences
8. Christrup et al. [11]	Randomized controlled clinical trial	18 patients	–	Sustained attention and vigilance	Continuous reaction time	No differences
9. Sjøgren et al. [44]	Cross-sectional	Patient groups: 1) 40 able to work/no pain/no opioid 2) 19 unable to work/no pain/no opioid 3) 19 unable to work/pain/no opioid 4a) 31 unable to work/pain/opioid 4b) 21 unable to work/no pain/opioid	no/nc	Sustained attention, psychomotor speed, working memory	Continuous reaction time, finger tapping test, Paced auditory serial addition task	No differences
10. Kamboj et al. [23]	Randomized controlled clinical trial	14 patients with malignant and non-malignant pain in sustained-release opioids	–	Attention, working/ immediate/delayed memory, phonemic fluency, psychomotor speed	Prose recall, digit span, everyday attention, map search, telephone search, elevator counting, elevator counting with distraction, verbal fluency, trail making task, finger tapping, mood rating scale	Anterograde and retrograde memory impairment

no no statistically significant difference, *nc* not controlled for (comparison not described in the study)
– same patients compared in different phases

Table 5 Correlations between cognitive function and other variables

Study	Age (years) mean/ variation	Educational level	Comparison	Opioid	Equivalent dose in morphine mean or variation	moment of assessment	Correlations
1. Bruera et al. [9]	56.0 58.0	Minimum 8 years (both groups)	Stable dose vs. dose increase	Morphine/ hydromorphone/ oxycodone/codeine	Stable 16.3 mg (parenteral) Increase 15,8 mg (parenteral)	Before and 45 min after morning dose	–
2. Sjøgren et al. [42]	58.5 56.0	–	Patients vs. healthy	Morphine	130–400 mg/d (oral) 32–240 mg/d (epidural)	45–375 min after last dose	Not significant
3. Banning et al. [4]	33.0–71.0 27.0–64.0	–	Patients vs. healthy	Morphine	30–920 mg/day	60–380 min after last dose	Sedation/analgesia and sustained attention (r=0.374, P=0.03)
4. Banning et al. [5]	33.0–71.0 38.0–73.0	–	Patients in opioids vs. patients without opioids	MorphineSR/ ketobemidone/ hydromorphone/ nicomorphine	30–400 mg/d	60–400 min after last dose	–
5. Sjøgren et al. [43]	23.0–71.0 27.0–73.0	–	Patients vs. healthy	Morphine IM/morphine SR/ketobemidone/ hydromor-phone/ nicomorphine	9–23 mg/d (IM) 30–920 mg/d (oral) 12–600 mg/d (epidural)	25–75 min after last dose	Sedation and sustained attention (r=0.372, P=0.04)
6. Vainio et al. [47]	53.0 51.0	Majority in both groups on basic level	Patients in pain/opioids vs. in pain/without opioids	Morphine	209 mg/d	90 min after last dose	Plasma morphine and metabolites and poor attention/structuring ability (r=0.61 to0.93, P<0.001–0.050)
7. Clemons et al. [12]	61.0 65.0 62.0	Majority uneducated	Patients in opioids vs. without opioids vs. healthy	Morphine	50–200 mg/day	90 min after last dose morphine solution and 4 h after controlled-release morphine	–
8. Christrup et al. [11]	54.0–69.0	–	Cross-over patients (opioid/ placebo phase)	Morphine SR/IR	40–600 mg/d	Before and 1, 2, 4, 6, 10, 12 h after dose	Not significant
9. Sjøgren et al. [44]	62.5 63.0 58.0 59.0 60.0	–	Patients able to work/no pain/no opioid vs. unable to work/no pain/no opioid vs. unable to work/pain/no opioid vs. unable to work/pain/opioid vs. unable to work/no pain/opioid	–	20–420 mg/day	180 –120 min after last dose	Not significant
10. Kamboj et al. [23]	65.2	11.4 years (mean)	Cross-over patients (SR opioid/placebo phase)	Morphine/diamorphine/ methadone/fentanyl	30–800/d	Before and 45 min after dose	–

IR immediate release, *SR* controlled/sustained release, *IM* intramuscular, – not mentioned

Table 6 Level of evidence and grade of recommendation according to study design

Database	Study	Design	Cognitive function	Level of evidence	Grade of recommendation
1. PubMed	Christrup et al. [11]	Randomized controlled clinical trial	No difference	2b	
2. Hand search	Kamboj et al. [23]	Randomized controlled clinical trial	Worsening	2b	
3. Hand search	Bruera et al. [9]	Controlled clinical trial	Worsening	2b	
4. Hand search	Sjøgren et al. [42]	Controlled clinical trial	Worsening	2b	
5. EMBASE	Banning at al. [4]	Cross-sectional	Worsening	2c	B
6. EMBASE	Banning et al. [5]	Cross-sectional	Worsening	2c	
7. EMBASE	Sjøgren et al [43]	Cross-sectional	No difference	2c	
8. EMBASE	Vainio et al. [47]	Cross-sectional	Worsening and improvement	2c	
9. EMBASE	Sjøgren et al. [44]	Cross-sectional	No difference	2c	
10. Hand search	Clemons et al. [12]	Case-control	No difference	4	C

results indicated that long-term morphine therapy had only a slight effect on functioning related to vehicle driving. The cognitive effects of pain were not reported.

In another cross-sectional study, Clemons et al. [12] examined seven advanced cancer patients on stable oral morphine and compared them with six advanced cancer patients not on opioids and with 16 healthy. Age and educational level were similar between groups, but there were no statistical calculations. A comprehensive test battery was used measuring IQ, memory, grammatical reasoning, reaction time, and a test of attentional capacity (*Stroop task*). The study indicated that cancer patients performed less well than healthy controls on all assessments, but neuropsychological tests did not demonstrate differences related to opioid treatment. Subjective measures showed a decreased feeling of alertness and attentional capacity on those on morphine compared to other groups, suggesting that the opioid contribution to the poorer cognitive performance was superimposed on the effect of the cancer disease process. However, due to the low number of patients, and additional use of adjuvant drugs in some of the patients, the results should be interpreted with caution.

Eighteen cancer patients completed a randomized, balanced, double-blind, double-dummy, two-period cross-over trial comparing the administration of immediate release tablets (every 6 h) with sustained release morphine (every 12 h) [11]. Identical total daily doses of morphine were given in both study periods and testing (CRT), and blood sampling was done on the study days 4 and 8 prior to the morning dose and several times after morphine administration. In steady state, day 4 and day 8, no statistically significant differences could be demonstrated between the treatments concerning CRT, sedation, pain, and side effects. The lack of statistically significant differences could be attributed to a small sample size.

A study of 130 consecutive cancer patients investigated the possible influence of long-term oral opioid therapy, pain, and KPS (KPS A, 80%–100%—able to carry on normal activity and work, and KPS B, 50%-70%—unable to work, able to live at home and care for most personal needs) on CRT, FTT, and *Paced auditory serial addition task* (PASAT) [44]. There were no statistically significant differences between the groups regarding age; however, educational level was not described. The design was cross-sectional, but a hierarchy of clinical relevant stigmatizing factors was devised in order to mimic progression of disease (Table 4). However, it should be noted, that group 4a was more stigmatized than group 4b as those patients were in pain and received higher stable doses of oral opioids. Group 1 constituted the control group and all other groups performed statistically significantly poorer than group 1 in one or more tests. Group 4a differed most significantly in the number and severity of poorly performed tests. In order to gain more information about the possible influence of pain and oral opioid treatment on neuropsychological performance, all groups being in KPS B were analyzed as follows: the non-opioid treated groups 2 and 3 (n=38) versus the opioids-treated groups 4a and 4b (n=51) did not show statistically significant differences in the three tests, whereas the pain-relieved groups 2 and 4b (n=40) versus the pain-suffering groups 3 and 4a (n=49) showed statistically significantly better performance in PASAT. Regarding the role of opioids and pain, the results indicated that the use of long-term oral opioid treatment in cancer patients per se did not affect any of the neuropsychological tests and that pain itself may deteriorate the performance of PASAT.

Increase of the daily dose

Bruera et al. [9] carried out a longitudinal opioid dose increase study in 40 cancer patients receiving intermittent opioids orally or parenterally. Twenty patients were in stable opioid dosing for at least 7 days, and 20 patients had undergone an increase of at least 30% in dose less than or equal to 3 days before admission to the study. There was no statistical comparison regarding age and educational level between groups; however, the authors stated that they had similar age and minimum of 8 years of scholarity. For two consecutive days, cognitive and psychomotor tests consisting of FTT, arithmetics, reverse memory of digits, and visual memory were performed in all patients before and after their morning dose (Tables 3 and 4). The results showed that significant cognitive and psychomotor impairment occurred in all tests immediately following a clinically relevant dose increase. Based on the absence of cognitive impairment in the group receiving stable dosing, the authors concluded that tolerance develops to cognitive effects.

Supplemental short-acting opioids on top of regular daily dose

A randomized, placebo-controlled, double-blind crossover study recently studied the cognitive effects of supplemental oral morphine administered on demand to 14 patients in palliative care on stable long-term opioid treatment [23]. The study did not investigate the effects of oral on-demand morphine in patients while they were experiencing breakthrough pain. Oral on-demand morphine reduced pain, produced transient ante- and retrograde memory impairments (*Prose recall*), and a decrement in the two tracking of *Trail Making Test* (Tables 3 and 4).

Opioids administered by alternative routes and opioid rotation

The terms "opioid switching" or "opioid rotation" relate normally to a treatment strategy, where a shift in the type of oral opioid takes place in order to improve analgesia and/or reduce opioid toxicity including sedation and drowsiness [13, 34]. However, these terms may also relate to both change of opioid type and administration route.

In an open crossover study, CRT, pain intensity and sedation were assessed in 14 cancer patients with insufficient pain relief during stable long-term (>2 weeks) oral opioid therapy followed by stable (1–2 weeks) epidural morphine therapy. Comparisons were made with 20 healthy controls also assessed by the same measurements [42]. Age differences were tested between groups and no difference was found. There was no information regarding educational level. Patients did not change KPS or pain types between the two evaluations. No statistically significant differences were found in CRT, pain, and sedation before and after initiation of epidural opioids, indicating that the advantage of epidural administration seems questionable at this dose level (Tables 3 and 4). However, due to the small sample size the results should be interpreted with caution.

Morphine metabolism

For the completion of this review, the cognitive effects of morphine metabolites measured by neuropsychological testing are also addressed.

Two earlier mentioned studies [11, 43] attempted to investigate the relationship between CRT and morphine and metabolite concentrations in plasma (Tables 3 and 4). The first study analyzing morphine concentrations by means of the radioimmunoassay method in eight patients receiving oral morphine, in eight patients receiving epidural morphine, and in eight patients receiving intramuscular morphine did not find any significant correlations between morphine concentrations and the performance of CRT; however, there was a correlation between higher sedation scores and longer continuous reaction times[43]. The second study analyzed steady-state concentrations of morphine, M6G, and M3G by high-performance liquid chromatography, in 18 patients on immediate release and sustained release morphine, respectively. There were no significant correlations between concentrations or concentration ratios of morphine, M6G, and M3G, respectively, and CRT on the two different administration forms [11].

In contrast to these findings, Vainio et al. [47] analyzed morphine, M6G, and M3G in 24 cancer patients on long-term oral morphine tested with a comprehensive test battery for professional vehicle drivers and found a positive correlation between plasma concentrations of morphine and its glucuronides and impairment in neuropsychological tests of attentional capacity, and of concentration and structuring ability (Tables 3 and 4).

Discussion

In the view of the complexity and variety of factors that can affect cognition, it is not surprising that there is a paucity of studies that selectively evaluates the cognitive effects of opioids in the cancer population. Concerns about the cognitive effects of opioids in patients with cancer pain are relative new and the scientific efforts in this field are relatively sparse. Thus, the first controlled trials appeared just two decades ago. Possibly, the severity of cancer and limited treatment alternatives in the past, which resulted in short life expectancy, were factors that may have reduced the worries about the cognitive side effects of opioids.

Recently, there has been an increasing focus on the cognitive sequelae that can result from cancer and its treatments. The importance of unpacking etiologies 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 etiology (amphetamine derivatives, metylphenidate, modafinil, corticosteroids, hydration, erythropoietin, blood transfusion, etc). Furthermore, complaints of cognitive impairment are often observed in pain patients in clinical practice [32].

In this review, according to the Oxford Centre for Evidence-based Medicine, the majority of studies were classified at level of evidence 2b and 2c, which indicate a moderate grade of recommendation (B). However, these studies did not perfectly fit the evidence classification, which, to some extent, seems to be inaccurate. The studies had limitations that could interfere in the quality of results and may cause bias. Most of them included convenience samples and were composed by too small patient samples. Furthermore, the control groups were not always adequate, as, e.g., healthy volunteers did not control for the cognitive effects of disease, and the educational level was most often not included and controlled for, despite the fact that it may influence cognitive performance [29]. Finally, in many studies the assessment was performed in patients who were already in opioid treatment (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 progression of disease and the development of tolerance to the effects of opioids.

Regarding cognition, the majority of studies have focused on oral opioid treatment, considering that the oral route is mainstay of cancer pain management. Seven studies [4, 5, 12, 42–44, 47] of this review were performed with patients in stable opioid treatment compared with controls without opioid treatment, which is an alternative and realistic design when baseline data, before opioid treatment, are not achievable. Some degree of cognitive deterioration ascribed to opioid treatment was observed in most of the studies, and the studies about dose increase and supplemental short-acting opioids reinforced the hypothesis that cognitive function can be sensitive to dose increments, although tolerance to cognitive effects may develop after some time [9, 10]. However, in two studies patients contemporarily treated with psychotropic drugs were included [12, 23]. Cancer patients in pain will often use combinations of opioids and adjuvant analgesics as antidepressants and/or anticonvulsants.

Pain medications, other drugs and different modalities of cancer treatment, for example current or former chemotherapy, may contribute directly to cognitive dysfunction or may indirectly make patients vulnerable to the opioid effects, slowing mental processing or reducing alertness [8, 18, 21, 48, 50]. Regarding pain, there is a disseminated idea that pain itself may cause cognitive impairment [44]. On the other hand, pain may also, as a mental stressor, antagonize the sedative effects of opioids. The latter has been indicated in chronic non-malignant pain patients [30]. Anxiety and/or depression are emotional disorders that frequently accompany long-lasting pain and cancer, and can have demonstrable adverse cognitive effects, most specifically on speed of mental processing and attentional functions. Anxiety effects involve slowed mental processing and blocked thoughts, and complaints of memory deficits. Depression may lower cognitive performance in many aspects, but major dysfunction can appear on tests of executive functions, processing speed, attention, and memory [1–3]. In the present review, only two studies assessed mood [12, 23]; however, no associations between mood and cognitive function were found.

In relation to cognitive effects of opioids administered by other routes, there is a pronounced lack of information. In cancer patients, the step-wise clinical practice, World Health Organization ladder [53], may oppose the possibilities of randomization between treatments. However, a possible solution is to compare the parenteral route with the spinal route using continuous infusions. Since these two modalities are widely accepted as alternatives, randomized prospective crossover designs would be possible. 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.

Furthermore, in this review we have included studies that analyzed associations between opioid dose, metabolite concentrations, and cognitive performance. Some enthusiasm concerning morphine pharmacokinetics and pharmacodynamics was noted in the late nineties. Only one study out of three studies found associations between concentrations of morphine and its metabolites and cognitive deficits [47]. Other uncontrolled studies—not included in this review—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 [52]. In contrast, a study with larger sample (n=298) did not demonstrate associations between morphine metabolites and cognitive function measured by the Mini Mental State Examination [MMSE] [25]. The 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 [45]. Although, the MMSE has gained enormous popularity in palliative care, criticism has been raised toward this instrument regarding its sensitivity [35].

The literature generally supports the use of neuropsychological tests measuring attentional capacity, psychomotor speed, speed of information processing, and short-term memory. It is a major challenge for clinical investigators in pain clinics and palliative care units to collaborate with clinical psychologists in developing and/or selecting an appropriate range of tests to improve the evaluation of disease-related and iatrogenic cognitive impairment. Especially quick, reliable bedside tests are needed. Validity studies of the neuropsychological tests defining cut points in cancer patients could enhance the clinical utility of the tests, and it is desirable that the tests have "ecological validity," which implicates correlations with everyday mental functioning. The latter is an important question as the cognitive deficits measured by neuropsychological testing in the cancer populations cannot readily be "translated" into everyday tasks such as car driving, operating machinery, looking after children, etc. Finally, the influence of cognitive dysfunction on quality of life is virtually unknown.

Significant factors that influence cognition have been identified, but due to the great variety of study designs and tests used, the specific nature and the quality of the cognitive impairment are still unclear. Other literature reviews with different characteristics had the same opinion that we need more refined research to explore the implications of opioids in cognitive function [10, 17, 26, 54]. To improve research in this area, future studies must include experimental designs, randomized 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 that can be associated with activities of practical life. 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), and 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

Very few controlled studies were identified and the majority of the studies showed minor cognitive deficits associated with long-term opioid use. These deficits were captured with neuropsychological measurements techniques, and their clinical implications and relevance on functional daily life are still unknown. Cognitive impairment was also associated with dose increase and supplemental doses of short-acting opioids. The increased longevity of cancer patients due to improved anticancer treatment efficacy has enhanced the importance of preserving cognitive function in those patients. Therefore, the cognitive effects of opioids and their consequences for cancer patients' quality of life deserve to be studied more comprehensively by randomized controlled trials with longitudinal designs.

References

1. Airaksinen E, Larsson M, Lundberg I, Forsel L (2004) Cognitive functions in depressive disorders: evidence from a population-based study. Psychol Med 34(1):83–91. doi:10.1017/S0033291703008559
2. Airaksinen E, Larsson M, Forsell Y (2005) Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. J Psychiatr Res 39 (2):207–214. doi:10.1016/j.jpsychires.2004.06.001
3. Austin MP, Mitchell P, Goodwin GM (2001) Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry 178:200–206. doi:10.1192/bjp.178.3.200
4. Banning A, Sjøgren P (1990) Cerebral effects of long-term oral opioids in cancer patients measured by continuous reaction time. Clin J Pain 6:91–95. doi:10.1097/00002508-199006000-00005
5. Banning A, Sjøgren P, Kaiser F (1992) Reaction time in cancer patients receiving peripherally acting analgesics alone or in combination with opioids. Acta Anaesthesiol Scand 36:480–482
6. Barsevick AM, Whitmer K, Nail L, Beck SL, Dudley WN (2006) Symptom cluster research: conceptual, design, measurement, and analysis issue. J Pain Symptom Manage 31(1):85–95. doi:10.1016/j.jpainsymman.2005.05.015
7. Barsevick AM (2007) The concept of symptom cluster. Semin Oncol Nurs 23(2):89–98. doi:10.1016/j.soncn.2007.01.009
8. Bender CM, Sereika SM, Berga SL, Vogel VG, Brufsky AM, Paraska KK et al (2006) Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology 15:422–430. doi:10.1002/pon.964
9. Bruera E, Macmillan K, Hanson J, MacDonald RN (1989) The cognitive effects of the administration and narcotic analgesics in patients with cancer pain. Pain 39:13–16. doi:10.1016/0304-3959(89)90169-3
10. Chapman SL, Byas-Smith MG, Reed BA (2002) Effects of intermediate and long-term use of opioids on cognition in patients with chronic pain. Clin J Pain 18:S83–S90. doi:10.1097/00002508-200207001-00010
11. Christrup LL, Sjøgren P, Jensen N-H, Banning AM, Elbæk K, Ersbøll AK (1999) Steady-state kinetics and dynamics of morphine in cancer patients: is sedation related to the absorption rate of morphine? J Pain Symptom Manage 18:164–173. doi:10.1016/S0885-3924(99)00068-8
12. Clemons M, Regnard C, Appleton T (1996) Alertness, cognition and morphine in patients with advanced cancer. Cancer Treat Rev 22:451–468. doi:10.1016/S0305-7372(96)90026-2
13. de Stoutz ND, Bruera E, Suarez-Almazor M (1995) Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 10:378–384. doi:10.1016/0885-3924(95)90924-C
14. Derogatis LR, Morrow GR, Fetting J, Penman D, Piasetsky S, Schmale AM et al (1983) The prevalence of psychiatric disorders among cancer patients. JAMA 249:751–757. doi:10.1001/jama.249.6.751
15. Dodd MJ, Janson S, Facione N, Faucett J, Froelicher ES, Humphreys J et al (2001) Advancing the science of symptom management. J Adv Nurs 33(5):668–676. doi:10.1046/j.1365-2648.2001.01697.x
16. Elsass P (1986) Continuous reaction times in cerebral dysfunction. Acta Neurol Scand 73:1–22

17. Ersek M, Cherrier MM, Overman SS, Irving GA (2004) The cognitive effects of opioids. Pain Manag Nurs 5(2):75–93. doi:10.1016/j.pmn.2003.11.002
18. Falleti MG, Sanfilippo A, Maruff P, Weih L, Phillips KA (2005) The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. Brain Cogn 59(1):60–70. doi:10.1016/j.bandc.2005.05.001
19. Fletcher RH, Fletcher SW, Wagner EH (2005) Clinical epidemiology: the essentials, 4th edn. Lippincott Williams & Wilkins, Baltimore
20. Gronwall D, Wrightson P (1974) Delayed recovery of intellectual function after minor head injury. Lancet 304(7881):605–609. doi:10.1016/S0140-6736(74)91939-4
21. Jansen CE, Miaskowski C, Dodd M, Dowling G, Kramer J (2005) A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. Cancer 104(10):2222–2233. doi:10.1002/cncr.21469
22. Jensen AR, Rohwer WD Jr (1966) The stroop color-word test: a review. Acta Psychol (Amst) 25:36–93. doi:10.1016/0001-6918(66)90004-7
23. Kamboj SK, Tookman A, Jones L, Curran HV (2005) The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. Pain 117:388–395. doi:10.1016/j.pain.2005.06.022
24. Klepstad P, Hilton P, Moen, Fougner B, Borchgrevink PC, Kaasa S (2002) Self-reports are not related to objective assessment of cognitive function and sedation in patients with cancer pain admitted to a palliative care unit. Palliat Med 16:513–519. doi:10.1191/0269216302pm587oa
25. Klepstad P, Borchgrevink PC, Dale O, Zahlsen K, Aamo T, Fayers P et al (2003) Routine drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients. Palliat Med 17:679–687
26. Lawlor PG (2002) The panorama of opioid-related cognitive dysfunction in patients with cancer. Cancer 94(6):1836–1853. doi:10.1002/cncr.10389
27. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME et al (2000) Occurrence, causes, and outcome of delirium in advanced cancer patients: a prospective study. Arch Intern Med 160:786–794. doi:10.1001/archinte.160.6.786
28. Levine PM, Silberfarb PM, Lipowski ZJ (1978) Mental disorders in cancer patients a study of 100 psychiatric referrals. Cancer 43:1385–1391. doi:10.1002/1097-0142(197809)42:3<1385::AID-CNCR2820420349>3.0.CO;2-0
29. Lezak MD (1995) Neurobehavioral variables and diagnostic issues. In: Lezak MD (ed) Neuropsychological assessment, 3rd ed. Oxford University Press, New York, pp 277–331
30. Lorenz J, Beck H, Bromm B (1997) Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. Pain 73:369–375. doi:10.1016/S0304-3959(97)00123-1
31. Massie MJ, Holland J, Glass E (1983) Delirium in terminally ill cancer patients. Am J Psychiatry 140:1048–1050
32. McCracken LM, Iverson GL (2001) Predicting complaints of impaired cognitive functioning in patients with chronic pain. J Pain Symptom Manage 21(5):392–396. doi:10.1016/S0885-3924(01)00267-6
33. McNamara P (2002) Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care. Palliat Med 16:425–434. doi:10.1191/0269216302pm536oa
34. Mercadante S, Casuccio A, Fulfaro F, Groff L, Boffi R, Villari P et al (2001) Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. J Clin Oncol 19:2898–2904
35. Meyers CA, Wefel JS (2003) The use of the Mini-mental State Examination to assess cognitive functioning in cancer trails: no ifs, ands, buts, or sensitivity. J Clin Oncol 21:3557–3558. doi:10.1200/JCO.2003.07.080
36. Pereira J, Hanson J, Bruera E (1997) The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 79:835–842. doi:10.1002/(SICI)1097-0142(19970215)79:4<835::AID-CNCR21>3.0.CO;2-#
37. Peters M (1976) Prolonged practice of a simple motor task by preferred and non-preferred hands. Percept Mot Skills 42:447–450
38. Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al (1998) Oxford centre for evidence-based medicine levels of evidence. http://www.cebm.net/index.aspx?o=1047. Accessed 11 January 2007
39. Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills 8:271–276
40. Santos CMC, Pimenta CAM, Nobre MRC (2007) The PICO strategy for the research question construction and evidence search. Rev Latino Am Enfermagem 15(3):508–511
41. Sjøgren P (1997) Psychomotor and cognitive functioning in cancer patients. Acta Anaesthesiol Scand 41:159–161
42. Sjøgren P, Banning A (1989) Pain, sedation and reaction time during long-term treatment of cancer patients with oral and epidural opioids. Pain 39:5–11. doi:10.1016/0304-3959(89)90168-1
43. Sjøgren P, Banning A, Christensen CB, Pedersen O (1994) Continuous reaction time after single dose, long-term oral and epidural opioid administration. Eur J Anaesthesiol 11:95–100
44. Sjøgren P, Olsen AK, Thomsen AB, Dalberg J (2000) Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status. Pain 86:237–245. doi:10.1016/S0304-3959(00)00248-7
45. Strömgren AS, Goldsmidt D, Groenvold M, Petersen MA, Jensen PT, Pedersen L et al (2002) Self-assessment in cancer patients referred to palliative care: a study of feasibility and symptom epidemiology. Cancer 94:512–520. doi:10.1002/cncr.10222
46. Stiefel FC, Holland JC (1991) Delirium in cancer patients. Int Psychogeriatr 3:333–336. doi:10.1017/S1041610291000789
47. Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E (1995) Driving ability in cancer patients receiving long-term morphine analgesia. Lancet 346:667–670. doi:10.1016/S0140-6736(95)92281-4
48. Vardy J, Rourke S, Tannock IF (2007) Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 25:2455–2463. doi:10.1200/JCO.2006.08.1604
49. Ventafridda V, Ripamonti C, DeConno F, Tamburini M, Cassileth BR (1990) Symptom prevalence and control during cancer patients last days of life. J Palliat Care 6:7–11
50. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA (2004) The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer 100(11):2292–2299. doi:10.1002/cncr.20272
51. Wilson B, Cockburn J, Baddeley A (1985) The Rivermead behavioural memory test. Thames Valley Test, Titchfield
52. Wood MM, Ashby MA, Somogyi AA, Fleming BG (1998) Neuropsychological and pharmacokinetic assessment of hospice inpatients receiving morphine. J Pain Symptom Manage 16:112–120. doi:10.1016/S0885-3924(98)00043-8
53. World Health Organization (2007) WHO's pain relieve ladder. http://www.who.int/cancer/palliative/painladder/en/. Accessed 12 December 2007
54. Zacny JP (1995) A review of the effects of opioids on psychomotor and cognitive functioning in humans. Exp Clin Psychopharmacol 3(4):432–466. doi:10.1037/1064-1297.3.4.432