The effects of opioids on cognition in older adults with cancer and chronic non-cancer pain: A systematic review

Sophie Pask[1], Myriam Dell'Olio[2], Fliss E. M. Murtagh[1] and Jason W. Boland[1]

[1] Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, United Kingdom.

[2] Academy of Primary Care, Hull York Medical School, University of Hull, United Kingdom.

Corresponding author: Sophie Pask (hysp1@hyms.ac.uk)

Wolfson Palliative Care Research Centre, Hull York Medical School, Allam Medical Building, University of Hull, Hull, HU6 7RX.

Number of tables: 4

Number of figures: 2

Number of references: 102

Word count: 6,546 (excluding abstract, figures, tables, references and title page)

Abstract

Context

Opioids are prescribed to manage moderate to severe pain and can be used with older adults; however, they may lead to several adverse effects, including cognitive impairment.

Objective

To identify, appraise and synthesise evidence on i) the impact of opioids on cognition in older adults with cancer/chronic non-cancer pain, and ii) screening tools/neuropsychological assessments used to detect opioid-induced cognitive impairment.

Methods

A systematic literature review following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PROSPERO Registration CRD42018092943). MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane Library and Web of Science were searched up to December 2018. Randomised controlled trials, quasi-experimental studies and observational studies of adults aged ≥65 with cancer/chronic non-cancer pain taking opioids were included. A narrative synthesis was conducted.

Results

From 4,036 records, 10 met inclusion criteria. Five studies used one screening tool and five used a range of neuropsychological assessments; assessing 14 cognitive domains. Most studies demonstrated no effect of opioid use on cognitive domains, whilst four studies showed mixed effects. In particular, attention, language, orientation, psychomotor function and verbal working/delayed episodic memory were worsened. Changes to cognitive function were predominantly observed in studies with higher mean doses of opioids (120mg–190.7mg oral morphine equivalent daily dose).

Conclusion

Both improvements and impairments to cognition were observed in studies with higher mean opioid doses. In clinical practice, a brief screening tool assessing attention, language, orientation, psychomotor function, and verbal working/delayed episodic memory, may be beneficial to detect worsening cognition in older adults with chronic pain using opioids.

249/250 words

Key words: Opioids, cognition, cancer, chronic pain, pain, elderly, systematic review

Introduction

Chronic pain is a common problem for older adults (≥65 years old), affecting at least 50% in the community and 80% in care homes (1, 2). Persistent pain, often moderate to severe intensity, in older adults is frequenty attributed to cancer and chronic non-cancer conditions (2-6). Pain can have a pronounced impact on older adults' independence, social engagement, ability to self-care and quality of life (7-10). Yet, it is often under assessed and poorly managed in this group (1).

Opioids are used to manage moderate to severe pain (11) and can be used with older adults when they have pain despite other treatments (2, 12). Short-term opioid use has some benefit in older adults with chronic non-cancer pain (13, 14). On the other hand, studies on the safety and efficacy of the long-term use of opioids in older adults are limited (13-16). Evidence suggests that it is unlikely to benefit and may be harmful to those with chronic non-cancer pain (15, 17, 18). Effective opioid therapy is dependent on the balance between analgesic effectiveness and adverse effects (19). Opioid use can lead to a number of adverse effects that impact gastrointestinal, neurological, cardiovascular, pulmonary, urological, endocrinological and immune systems; including cognitive impairment (20-25). Although these adverse effects are common for all age groups, older adults are at greater risk due to comorbidities and polypharmacy (20). In particular, older adults can experience high medication burden and risk of drug interactions (9, 26-28). Developing our understanding of opioid-related risks in older adults is necessary (29-31), including how we can effectively screen for opioid-related issues (2, 30).

Opioid-induced cognitive impairment can lead to a reduced attention span, disorientation regarding time, restlessness, agitation, hallucinations and delirium (32). All of which can have a pronounced impact on older adults' and their carers' quality of life (32). Concerns about these issues can also affect healthcare professionals' initiation of opioid therapy (33). Opioid use and its impact on cognitive function in older adults is understudied. The evidence base largely focusses on adult cancer and chronic non-cancer populations, without focus to older adults (34-38). Previous systematic reviews of the evidence on older adults have focussed on postoperative cognitive impairment (39) or opioids for the management of chronic non-cancer pain (40). Understanding the relationship between cognition, opioids and pain management in older adults' is important in enhancing knowledge of healthcare

professionals to guide clinical practice, as well as improving patients and carers understanding of opioids (41, 42). Additionally, systematic identification and assessment of cognitive impairment could be useful in guiding opioid therapy. However, there is little consensus on which tools and assessments are effective in identifying cognitive impairment and which cognitive domains are impacted by opioids (34, 43, 44).

Therefore, the aim of this systematic review was to identify, appraise and synthesise the:

i) Evidence on the impact of opioids on cognition in older adults with cancer and chronic non-cancer pain.

ii) Screening and assessment tools that have been used to detect and assess opioid-induced cognitive impairment, and to discuss their usefulness for identifying cognitive issues in older adults.

Methods

The protocol for this systematic review was prepared according to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (45, 46) and registered with PROSPERO (CRD42018092943) prior to screening and data extraction (47). This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidance (48).

Search strategy

MEDLINE, EMBASE and PsycINFO (via Ovid), CINAHL Plus (now CINAHL Complete, via EBSCO), Cochrane Central Register of Controlled Trials in the Cochrane Library (via Wiley), Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Emerging Sources Citation Index, Conference Proceedings Citation Index – Science and Conference Proceedings Citation Index – Social Science & Humanities), ProQuest and OpenGrey databases were searched from inception to December 2018. Search terms were identified from existing reviews. Free text terms for searching titles, abstracts and key words were combined with database-specific MeSH terms that reflect the following aspects; [opioids] AND [cognition] AND [older adult population]

(see Appendix 1: Example of the full search strategy). No electronic limits were applied to database searches.

The reference lists of relevant systematic reviews and first author's EndNote library were screened to identify further studies that may not have been identified in the database searches. Where full-texts were not available or lacked information to confirm eligibility, authors were contacted.

Study selection

The studies returned from the search were imported into EndNote X8 and duplicates were removed. Titles and abstracts were screened for inclusion by two authors (SP and MD) independently in duplicate. For articles that potentially met inclusion criteria on title and abstract, SP and MD then assessed full-texts for eligibility. Disagreements between the two authors at all stages were resolved through discussion with a third reviewer (JB).

Table 1 lists the criteria for including studies. For the purpose of this review, older adults in this systematic review were defined by the chronological age of ≥65, as commonly adopted by most developed countries to describe older adults (49, 50).

Data extraction and analysis

SP and MD extracted data to electronic data extraction forms, independently in duplicate. Data extraction forms were crosschecked for accuracy and missing data. Data collected included general information (author and year, type of publication, country of origin, source of funding and conflicts of interest), study characteristics (aim, study design, inclusion and exclusion criteria, recruitment procedures and study duration), participant characteristics (number of participants, source and setting of population, age, gender, disease characteristics, comorbidities and concurrent medications), how cognitive impairment was assessed (screening tools and/or neuropsychological assessments) and other outcomes collected, details of opioid treatment (type, dose, route of administration and length of use), statistical analyses used, the effect of opioids on cognition, limitations, and conclusions.

Quality was independently assessed by two authors (SP and MD) using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields (QualSyst) 14-item checklist for quantitative studies (51). A summary score is calculated for each paper by dividing the total sum by total possible sum (51). In this systematic review, the reviewers used the calculated score to define the quality of papers as strong (score of >0.80), good (0.71–0.79), adequate (0.50–0.70) or poor (<0.50) and did not exclude on account of poor quality, in line with other systematic reviews (52, 53).

A narrative synthesis was used, guided by Popay and colleagues (54). A theory of how, why and for whom the intervention worked was not developed for this systematic review as previous reviews of a similar nature found variable effects on cognition after opioid use. An exploratory approach was used, with study design/methods, sample size, diagnosis, tools/assessments used, and opioid dose and length of use identified as factors to consider in the synthesis. Secondly, tabulation was used to develop a preliminary synthesis of included studies to aid interpretation of patterns across studies. Data regarding dose was transformed into oral morphine equivalent daily dose (MEDD) to enable dose comparison between studies. Thirdly, outcomes of tools and assessments were mapped against cognitive domains assessed to analyse similarities and differences across studies. Additionally, the cognitive outcomes were mapped against previously identified cognitive domains affected by chronic opioid use (namely cognitive flexibility, cognitive impulsivity and verbal working memory) (43), as well as 'additional' domains captured by the screening tool and neuropsychological assessments of included studies. Lastly, a critical reflection of the strengths and limitations on the robustness of the synthesis is included in the discussion.

Results

Study selection

A total 4,036 unique records were identified. Of these, 57 full-texts were screened and 10 were found eligible for inclusion (see Figure 1: PRISMA flowchart). For a summary of included studies see Table 2.

Study characteristics

Included studies were conducted in the United Kingdom (N=3), Italy (N=3), United States of America (N=3) and Finland (N=1). All studies were published in English. The studies comprised of three randomised controlled trials (55-57), six observational (58-63) and one quasi-experimental design (64). Four studies adopted the use of comparison groups to: (i) determine the efficacy of opioid use versus conventional therapy (55), (ii) assess the difference between central nervous system (CNS) medication users and controls (with opioid subgroup analyses) (60), (iii) determine the difference between opioid users and non-opioid users (61) and (iv) investigate whether opioids or the disease itself had an impact on cognition (64).

Population and settings

A total of 1,087 participants were included in the 10 studies. Changes to cognition from opioid use were explored by two studies in older adults with cancer pain (63, 64), six studies in older adults with chronic non-cancer pain (55, 57-59, 61, 62) and two studies that included both (56, 60). Across nine of the ten included studies (55-59, 61-64), 44 participants had cancer pain, 462 participants had chronic non-cancer pain (predominantly osteoarthritis and postherpetic neuralgia) and 16 participants were healthy controls. In Puustinen et al. (2011), diagnoses were only available for 156 CNS medication users and 243 CNS medication non-users of the 565 recruited. This included both cancer and non-cancer diagnoses. However, participants who were taking opioids only had diagnoses of painful arthritic diseases (60).

Study settings varied; two were conducted at a hospice (with one including both inpatients and outpatients) (63, 64). The other studies were conducted within a municipality (i.e. single urban area) (60) as well as a multi-centre ambulatory services (58), nursing home (55), palliative care unit (inpatient and outpatient) (56), pain treatment centre (62), an older pain management program (61) and rehabilitation centre (59). One study did not clearly specify a study setting but recruited participants through GP referral/advertisements (57).

Tools and assessments used to identify changes to cognition

Table 3 summarises the screening tool and neuropsychological tests used to identify and assess changes to cognition from opioid use, including a description, cognitive domains assessed and outcomes of the tests.

Type and combination

One screening tool and twenty-one neuropsychological assessments were used to identify changes to cognition from opioid use. Five studies (55, 58-60, 62) adopted the use of a screening tool (i.e. the Mini-mental State Exam; MMSE) in isolation and five studies (56, 57, 61, 63, 64) used a combination of neuropsychological tests. The MMSE was the most used instrument across all studies. Studies using neuropsychological assessments to assess cognition adopted different combinations of assessments. Clemons et al. (1996) stated that the National Adult Reading Test was resistant to the effects of drugs, whilst the Stroop-Colour Word Test was likely to give an indication of changes to cognition from opioid use (64). Kamboj and colleagues (2005) also acknowledged that the Prose Recall Test would be sensitive to opioid-induced recall impairments (56). The Cognitive Drug Research (CDR) computerised assessment used by McNamara and colleagues (63) was developed to assess effects from novel compounds on cognitive function, in both volunteers and patients in clinical drug development (65). Other studies did not discuss the tools/assessments relevance to detect opioid-induced cognitive impairment.

Administration

The timing of screening tool and neuropsychological assessment administration varied across studies. Most studies provided limited description around when tests were administered (80%, n=8) (55, 57-63). Those that provided more detailed information about administration generally provided timings in terms of hours or minutes after taking opioids to ensure that opioid plasma levels were at their peak and/or that the timing of tests remained consistent at each visit (56, 64). Nine of the ten studies measured cognition at baseline but follow-up periods ranged from 2 weeks to 52 weeks. Karp and colleagues

(2006) conducted neuropsychological assessments within 2 weeks of recruitment to minimise effects of newly prescribed treatments on the assessment outcomes (61).

Cognitive domains

Fourteen cognitive domains were covered by the tool and assessments (see Table 3). Cognitive domains captured include attention, cognitive flexibility (including verbal and non-verbal fluency), concentration, language, memory (both short-term and long-term, as well as speed of memory retrieval), orientation, pre-morbid IQ, psychomotor function, psychomotor sedation, psychomotor speed, reaction speed and reasoning.

Changes to cognition

There were mixed effects of opioids on cognition in older adults with cancer and chronic non-cancer pain (see Table 3). Four studies (112 participants taking opioids) (56, 60, 61, 63), demonstrated a change in cognition from opioid use when comparing the effects of morphine with a matched placebo (56), switching opioids (63) or between those who received opioid treatment and a control group comparison (60, 61). Control group comparisons consisted of non-opioid users (N=27) (61), and those using no CNS medication (N=384) and non-users of corresponding medications (N=556) (60). In six studies (233 participants taking opioids), no changes to cognition were observed from baseline to follow-up between groups (55, 64) or in a cohort of participants (57-59, 62). Sixteen healthy controls and six advanced cancer patients not taking opioids (64), and 33 participants receiving conventional therapy (i.e. acetaminophen, non-steroidal anti-inflammatory drugs, COX-2-Inhibitor) not taking opioids (55) were used as control group comparisons. In four of the ten included studies, exploring changes to cognition from opioid use was the primary outcome (56, 57, 60, 64), however, in six studies it was a secondary outcome (55, 58, 59, 61-63).

Mapping cognitive domains and outcomes to opioid use in older adults

As discussed above, studies assessed cognitive function using either a screening tool in isolation or a combination of neuropsychological assessments covering 14 cognitive domains. The screening tools and neuropsychological assessments used have been mapped against these different cognitive domains (see Figure 2). Of the three cognitive domains identified by Baldacchino and colleagues (43), the screening tool and neuropsychological tests of included studies all captured verbal working memory, whilst none captured cognitive impulsivity. Cognitive flexibility was captured by three studies (56, 61, 64). Delayed recall/long-term memory was the most common 'additional' domain covered by included studies, followed by attention, language, orientation, concentration, psychomotor function, psychomotor speed, memory retrieval speed, pre-morbid IQ, psychomotor sedation, reaction speed and reasoning.

Opioid treatment and concurrent medications

Opioids used varied across studies (see Table 4). Six studies (56-59, 63, 64) examined the use of one opioid only (including buprenorphine, fentanyl, morphine and oxycodone). Three studies (55, 60, 62) used more than one opioid (including: codeine, dextromethorphan, dextropropoxyphene, ethylmorphine, hydromorphone, morphine, methadone and oxycodone). Of which, two studies compared differences between drugs; including opioids in comparison to antidepressants (57) and between different opioids (oxycodone and codeine) (55). Whilst, one study included participants taking one of four opioids without comparison (62). Oral administration of opioids was most common, followed by transdermal patch and syringe driver. Two studies did not report route of administration (57, 60). Karp and colleagues (2006) did not provide detail around the type(s) of opioids used or route of administration (61).

MEDD across all studies ranged from 11.5mg to 190.7mg, with two studies not accounting for dose (60, 61). The length of use also varied from approximately 7 days to 72 weeks, with one study not accounting for length of use (61). In studies that demonstrated no difference to cognition, mean MEDD daily dose ranged from 11.5 to 104.29mg (55, 57-59, 62, 64), excluding the 13 participants that were provided with 15mg methadone (150mg MEDD) due to adverse effects from morphine (57). In studies that demonstrated a change to cognition,

mean MEDD were 190.7mg over an 11.7 day study period (56), 120mg – 240mg over a 14-day study period (63) and dose not taken into account when comparing baseline with a 7.6 year follow-up (60) or between opioid users versus non-opioid users, without consideration to dose or length of use (61). Pain relief was achieved at low daily doses of opioids in a number of studies without detriment to cognition (55, 57-59). Opioid switching also demonstrated improvements to patients' global assessment of wellbeing that were deemed clinically significant (63). One study found that pain worsened along with general wellbeing, mood and concentration (64).

The majority of studies provided some description around the use of multiple concurrent medications. Three studies reported that pain medications previously taken by patients were discontinued before study commencement (55, 57, 58). However, Gianni et al. (2011) specified that medications were only stopped if they lacked efficacy (58). Corsinovi et al. (2009) acknowledged that concurrent medications were taken at stable doses three weeks prior to the study and continued at stable doses (55). Other studies detailed that rescue medication was provided for breakthrough pain but the authors did not clearly specify if any other medications were taken (58, 63). Three reported the use of concurrent medications taken by participants at the time of testing (56, 62, 64), including opioids (64). Puustinen et al. (2011) aimed to capture the use of any CNS medication but provided different subgroup analyses (60). Two studies did not clearly report whether concurrent medications were taken (59, 61).

Risk of bias and reporting quality

The mean quality score for included papers was 0.77. There were three adequate-quality papers (61, 62, 64), two good-quality papers (58, 63) and five strong-quality papers (55-57, 59, 60). The randomised controlled trials demonstrated consistently high quality (strong; 0.82–0.93). Observational studies varied in quality, ranging from adequate to strong (0.55–0.91). The quasi-experimental study was adequate in quality (0.55). Two randomised controlled trials reduced chances of selection, performance and detection bias by using double-blind, placebo-controlled, randomised approaches (56, 57). Although, one did not provide detailed information around randomisation to treatment order and allocation

concealment (56). A single-blind approach lacked detail around random sequence generation and allocation concealment. However, chances of performance and detection bias were reduced by blinding the researchers to the intervention participants received (55). Other included studies may be susceptible to selection, performance and detection bias due to the absence of randomisation and blinding. All studies, where relevant, described attrition and exclusion from the analysis. Subject selection and sampling frames were not well-reported across most studies, along with power calculations to ensure whether the sample size was appropriate. Non-randomised studies often failed to control for confounding (58-64).

Discussion

This systematic review builds on previous reviews (34-37, 40) by focussing attention to the cognitive effects of opioids in older adults with cancer and chronic non-cancer pain. The current review also aimed to ascertain the screening and assessment tools used to identify changes to cognition from opioid use in this population. This complements recent systematic reviews and meta-analyses exploring the neuropsychological consequences of opioid use in adults with a chronicity of and/or dependent on opioid use (43) and long-term opioid use in adults with chronic non-cancer pain (44).

Opioid-induced cognitive impairment in older adults with cancer and chronic non-cancer pain

Mirroring previous systematic reviews on the cognitive effects of opioid use in adults with malignant and non-malignant pain (34-36), the current review found varied effects on cognition from opioid use, with six studies demonstrating no change to cognition from opioid use. Drawing together the findings from adult cancer populations (36) and chronic non-cancer populations (35), an updated review indicated that there was either no difference or worsening cognition in adult cancer patients and no difference or an improvement in cognition in chronic non-cancer populations (34). In the current review, a non-comparative study exploring domains of cognitive function in an older adult population

with cancer found that domains did not change (i.e. concentration, quality of secondary memory and psychomotor function) or improved (speed of memory retrieval and verbal working memory), although numbers were small (63). In another study with a predominantly cancer population, changes to cognitive domains were either not present (i.e. psychomotor sedation or verbal working memory), improved (i.e. cognitive flexibility), worsened (i.e. attention) or improved then worsened (i.e. psychomotor function) across the different neuropsychological assessments used (56), although again, the sample was small. Whilst in a study that explored cognitive changes from long-term opioid use in chronic non-cancer patients (i.e. patients with painful arthritic diseases) via a subgroup analysis, there was a decline in cognitive function (60). However, there was also very few participants. Karp and colleagues (2006) found that opioid users experienced more difficulty with unprompted memory compared to opioid users, in those with non-malignant pain (61). Nevertheless, the sample size and reporting around opioid use were limited. These findings contrast with previous reviews, with improvements to cognition detected in cancer populations and the decline of cognition in a chronic non-cancer population. However, methodological limitations, small sample sizes and variation in study design pose challenges to drawing definite conclusions from the included studies.

Dose increase was associated with impaired cognition in a previous systematic review (34). There is no definitive definition of 'high dose' in scientific literature (66); UK guidance states that the risk of harm increases at doses above 120mg/day without increased benefit (67). Changes to cognition in the current review were mostly observed in studies that adopted the use of higher mean opioid doses (i.e. 120mg – 190.7mg MEDD) (56, 63). However, Puustinen and colleagues (2011) demonstrated changes to cognition from long-term use of opioids, although dose was not taken into account (60). Karp and colleagues (2006) also found that unprompted memory was impaired in those who used opioids compared to those that did not, without taking dose into consideration (61). A number of studies found that low doses of opioids were a valid treatment for moderate to severe chronic pain without any associated cognitive impairment (55, 57-59, 62). Although, some studies considered to have a low mean dose demonstrated some wide ranges in dose, including higher doses (57, 58, 62). Transient improvements to short-term memory and memory retrieval speed were also observed after switching from morphine to fentanyl (63). Potential

benefits of opioid rotation and opioid switching (68) and the usefulness of fentanyl in comparison to morphine (69) were also recognised in excluded studies. However, a multi-national study on the prevalence and predictors of cognitive dysfunction in adult cancer patient demonstrated no difference in cognitive effects between three commonly used opioids (fentanyl, morphine, and oxycodone) (70). Although, this study used the MMSE, which may not have been sensitive enough to capture subtle differences to cognition. Overall, the type of opioids assessed and the doses used across studies varied greatly.

The previous reviews commented on the methodological weaknesses of studies assessing cognitive function in cancer and chronic non-cancer populations (34, 35, 71). The weaknesses identified were the use of non-randomised and non-controlled study designs, lack of suitable control groups as well as issues around the cognitive effects of pain itself, polypharmacy, and other confounders impacting on cognitive outcomes. These issues were also recognised within the current review. Studies that adopt a controlled design are thought to be of the highest quality (34). This review did not restrict by controlled design or study quality as there is limited evidence in this population and we aimed to be inclusive of all possible studies. Kendall et al. (2009) highlighted that changes to cognition varied between study designs (35). They found no difference to cognition or an improvement in RCTs and non-controlled comparative designs and no difference or worsened cognition in observational studies. Due to the limited number of included studies in this review and the small number of studies that detected a change in cognition, as well as the variety of study designs adopted, it was not possible to determine the role of study design in patterns of changes to cognition from opioid use. There are also challenges around the appropriateness of study design in this older adult population, such as long-term exposure to harmful effects of medications (60, 72, 73).

Impaired cognition is frequently associated with the pain or disease experience (74). The use of an appropriate control group is considered important as the use of healthy volunteers does not account for the effects of pain or the disease itself (34). An ideal control group would include older adults eligible for opioid therapy but not receiving the treatment (34). The prolonged use of a placebo or not providing suitable treatment could pose ethical issues but such methods can be beneficial if they adopt sound methodological considerations (56, 72, 73). One included study used older adults with advanced cancer not

taking opioids and healthy volunteers as control groups to determine the impact of opioids and the disease itself on cognition (64). However, the reporting of group differences in study outcomes were vague and differed between the results and discussion sections of the paper; making it challenging to interpret the impact of the disease itself and from the use of opioids. The control groups in the other studies consisted of conventional therapies without use of opioids (55), those not taking CNS medications or non-users of corresponding medications (60) and older adults not taking opioids (and unclear if they are eligible for opioid therapy) (61). Therefore, the control groups adopted in other studies did not best reflect controlling for appropriate risk factors in the context of opioid-induced cognition. Other included studies did not adopt a control group, although, two studies used participants as their own controls in cross-over designs (56, 57).

Older adults commonly take several concurrent medications (27). Older adults' cognition is susceptible to polypharmacy and anticholinergic burden from the use of multiple medications (75, 76). A longitudinal cohort study evaluating the combined use of multiple CNS medications (including opioids) in healthy older adults, excluded from this review, indicated that the combined use of CNS medications, particularly at high doses, were associated with cognitive decline in healthy older adults (77). We acknowledge that medications for a number of medical conditions may also impact on cognition. The cognitive effects of opioids from included studies are difficult to determine due to differences in or lack of controlling for the use of multiple medications in a number of studies (55-57, 60, 61, 63, 64), as well as unclear/poor reporting (58, 59, 61). This may explain some of the variability in the cognitive outcomes of included studies. By controlling for medications prior to study commencement or during, a better understanding of baseline cognition and opioid impact can be gained. Other confounding factors, such as degenerative cognitive impairment associated with age, should also be considered. Most included studies had signs of severe cognitive impairment or dementia (usually assessed by mini-mental state examination (MMSE) score) as an exclusion criterion (55-62).

More understanding around the effect of opioids on cognition in older adults with cancer and chronic non-cancer pain is still needed. Currently, there is a small number of studies available. The limitations of current evidence, due to the heterogeneity of results and

methodological approach, suggest that we need a more standardised approach, with clearer reporting.

Screening tools, neuropsychological assessments and cognitive domains

There are a wide variety of screening tools and neuropsychological assessments available but there is little consensus around a standardised approach to identifying and assessing changes to cognition from opioid use (34, 35, 71). In particular, there is limited understanding of which tools and assessments may distinguish clinically meaningful changes to cognition in older adults with cancer and chronic non-cancer pain. Determining which tool(s) and/or assessment(s) are appropriate in this population could provide an accurate way to detect changes to cognition over time and inform adjustments to treatment (35, 64).

The MMSE was the only screening tool identified and was predominantly used across included studies. The MMSE was designed for use with patients with dementia and is commonly used to assess cognitive function (78, 79). Despite wide acknowledgement in the literature that the MMSE lacks sensitivity to detect minor changes to cognition, it is still predominantly used as reasonably quick to administer and engrained in clinical practice (80-83). A significant association between cognitive decline (including attention, language, orientation and both short- and long-term memory) and opioid used was demonstrated in an observational longitudinal study included in the current review using the MMSE (60). However, the small number of participants using opioids and issues with adjusting for some risk factors (e.g. alcohol use) limits the interpretation and generalisability of these findings to other elderly populations. A large longitudinal study, using self-reports of cognition, explored the relationship between opioids on clinical outcomes for patients receiving palliative care, it found that opioid use was not related to worsened cognition in an adjusted analysis (84). Although, the authors acknowledged that the low cognitive symptom scores could have been due to the exclusion of low MMSE scores (i.e. ≤24) and that the included sample represented a group with lower risk of cognitive deterioration (84). Other included studies in this review that adopted the MMSE did not detect a difference. Evidence supports the use of other, more nuanced, brief screening tools subsequently developed to detect mild changes to cognition in older adults compared to the MMSE (79, 85, 86). The use of

alternative screening tools has been recognised in substance misuse research, including opioid misuse (87-89).

Neuropsychological effects from opioid use are well-documented (34, 35, 42-44, 71). Neuropsychological assessments can detect subtle changes to cognition from opioid use (90). However, we do not know if performance on neuropsychological tests relate to clinically relevant effects or recommendations (42, 43, 90). The single measure focus of neuropsychological tests (e.g. attention) is problematic in drawing conclusions around cognitive impairment from opioid use (42), as multiple domains appear to be affected. The included studies that adopted neuropsychological tests used multiple assessments to assess different cognitive domains. The Incidental Learning Tests (i.e. free recall), Prose Recall Test, Trail Making Task and subtests of the CDR computerised assessment detected changes to cognition (56, 61, 63). The use of multiple assessments may be challenging in clinical practice, as this would take significantly more time to perform (91). Tools to detect opioid-induced cognitive impairment in a primary care setting need to be comprehensive, easy to administer within a short time frame, valid and reliable (90).

A better understanding of the cognitive domains that are affected by opioid use in this older adult population could lead to the use of or development of a more suitable assessment tool and a clearer definition of what constitutes opioid-induced cognitive impairment. Baldacchino and colleagues (2018) identified cognitive flexibility, cognitive impulsivity and verbal working memory as important cognitive domains in adults using opioids chronically. A more recent systematic review and meta-analysis found that long-term opioid use in adults reduced attention compared to other treatments that targeted the central nervous system (44). All studies in the current review assessed verbal working memory; with one detecting an improvement using the CDR micro-computerised assessment (63) and one finding a decline to cognitive performance using the MMSE in this domain (60). Cognitive flexibility was only measured in three studies and assessed with five different neuropsychological assessments (56, 61, 64); with only the Trail Making Task (Task B-A) detecting an improvement in this domain (56). Attention was also found to be affected in a longitudinal population-based study that screened cognition using the MMSE (60). There are concerns regarding the ecological validity of neuropsychological assessments, in that, there is a lack of agreement around the constructs that some tests aim to measure, leading to

difficulties in interpreting the outcome (92). This may contribute to the varied findings across studies. Practice effects are also a recognised characteristic from completing multiple assessments, where test performance may be attributed to increased familiarity (93). Out of the included studies that conducted multiple assessments (55-60, 62-64), two discussed practice effects, whilst only one study controlled for them (57). Therefore, practice effects may have had influence over the cognitive outcomes.

None of the existing screening tools and neuropsychological assessments of included studies are suitable to evaluate all cognitive domains (94). Other domains that demonstrated cognitive change in the current systematic review included delayed episodic memory, language, orientation and psychomotor function. How we define opioid-induced cognition in older adults may need to consider additional cognitive domains (i.e. delayed recall/long-term memory and psychomotor function). However, due to the methodological designs of the studies, small sample sizes and populations included, there could be some noise around cognitive effects from opioids, such as issues of pain, the disease itself and the use of appropriate control groups. There may also be other cognitive domains to consider that have not been captured in the included studies. Limited reporting of the timing of administration may have also hindered understanding of whether the tools and assessments would detect a change in cognition due to opioids (e.g. ensuring opioid plasma levels were at their peak) (64).

Driving is a complex task that requires a range of cognitive skills (such as attention and executive functions), visuospatial skills, motor ability, and multisensory perception (95, 96). Previous reviews explored the impact of opioids on driving ability in adults with cancer and/or chronic non-cancer conditions as part of their assessment of opioid-induced cognitive impairment (35-38). The findings from these systematic reviews are limited due to the scarce number of studies available, as well as the absence of clinically relevant information and appropriateness of tests to assess cognition and driving ability amongst chronic pain populations in terms of clinical practice and everyday tasks (36, 37). Studies assessing driving ability were considered within the current review, however, studies were not eligible for inclusion as study populations were under 65 years of age.

Clinically, opioid neurotoxicity in older adults often presents itself as sedation, confusion, as well as hallucinations, mood disorders and cognitive impairment (40, 42). The screening tool and neuropsychological assessments of included studies in this systematic review do not capture issues with some cognitive adverse effects, like hallucinations, and may not detect sedation and confusion in a clinically meaningful way. Yet, these are considered clinically important side effects (42, 97, 98) as well as impactful on patient wellbeing (99).

Strengths and limitations

This systematic review was guided by the PRISMA-P checklist (45, 46) to ensure that the protocol development and reporting were robust. Multiple search engines were searched (inclusive of language, publication status and publication date) to enable the identification of all possible literature. Another strength was our exclusion of studies where cognitive function may already be compromised either by existing health conditions (e.g. patients with dementia) or where patterns of opioid use were likely to differ (e.g. perioperative use or substance misuse).

There were several potential limitations. Studies that relied on self-report or clinical opinion, which may be of interest in clinical practice, were not included. However, the focus on formal screening tools and neuropsychological assessments allowed for ease of comparison with previous reviews. Another limitation was defining an older adult population. We used a chronological age of 65 and over; as commonly adopted by most developed countries and for providing a suitable cut-off value for inclusion (49, 50). We recognise that some included participants could be less than 65 and that chronological age does not account for individual patient characteristics/responses to prescribed medications (100). Most included studies consisted of chronic non-cancer pain populations, which may limit the generalisability of findings to cancer pain populations. Additionally, some studies may have been underpowered, as they explored changes to cognition from opioid use as a secondary outcome. This review adopted the QualSyst tool to assess study quality, as it allowed for the standardised, empirically grounded, assessment of a variety of study designs (51). However, it lacked the ability to identify specific biases, which may have led to inflated quality grades of included studies.

Overall, the methodological issues, small sample sizes and poor reporting in the included studies limits how we can interpret the effects from the opioids on older adults' cognition and the interpretation of the review findings. Therefore, this review does not make recommendations or implications for practice that go beyond the scope of the included evidence.

Implications for practice

This review highlights the absence of a standardised approach to assessing opioid-induced cognitive impairment in older adults with cancer and chronic non-cancer pain, and how current approaches adopted in research studies lack suitability. Therefore, the use of formal screening tools and neuropsychological assessments of opioid-induced cognitive impairment cannot replace clinical judgement and identifying clinically meaningful adverse effects, such as hallucinations. The use of formal screening tools should be seen as a guide to support clinical decisions. The MMSE does not appear to be discriminatory towards cognitive effects from opioid use. The use of a brief, more nuanced, screening tool that assesses attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory may be beneficial in practice compared to neuropsychological assessments in detecting opioid-induced cognitive impairment in this older adult population, as less time consuming to administer. However, an appropriate tool requires further assessment.

Recommendations for future work

This review has observed changes to some cognitive domains from opioid use in older adults with cancer and chronic non-cancer pain. In particular, attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory were worsened. Due to the small number of primary studies available and their limitations, future research should focus on determining the cognitive domains affected in this older adult population. Future primary research studies in this area should consider adopting cognition as a primary objective, larger sample sizes, clearer reporting around opioid use (type, dose,

route of administration and length of use) and provide more detail around the administration of screening tools and neuropsychological assessments used. This would also require determining the validity and reliability of existing screening tools and neuropsychological assessments to detect clinically meaningful changes, and other clinically important adverse effects not captured by current tools and assessments. The value of other screening tools, other than the MMSE, to detect cognitive change from opioid use in older adult populations with cancer or chronic non-cancer pain requires investigation.

Conclusions

The findings of this systematic review suggest effective pain relief may be achieved at low daily doses, without affecting cognition. Changes to cognition (including both improvements and impairments) were predominantly observed in studies with higher mean opioids doses (120mg–190.7mg MEDD). Attention, language, orientation, psychomotor function, and verbal working/short-term and delayed episodic memory were worsened by opioid use. As neuropsychological assessments are too cumbersome for use in clinical practice, a more nuanced brief screening tool with consideration to the cognitive domains identified may be beneficial. The MMSE does not appear discriminatory enough. A better understanding of cognitive impairment caused by opioids in this population could be used to inform adjustments to pain treatment and the benefit-risk balance of opioid use.

Author contributions

SP was responsible for the conception of this project, design of the study, acquisition and analysis of data for this article, as well as drafting and revision of the manuscript. JB and FM were responsible in the supervision of this project and helped to shape project conception, study design, and re-drafting the manuscript. JB also acted as a third reviewer and resolved any disagreements between the first and second reviewer. MD was responsible for acting as a second reviewer, screening records, extracting data and quality appraisal, as well as in the revisions of the manuscript. All authors approved the final draft.

Disclosure/Conflicts of interest

The authors have nothing to disclose.

Acknowledgements

The authors thank Fiona Ware of the University of Hull Library Team for her assistance in formulating the search strategy and Professor Ivana Markova (Professor and clinical consultant of neuropsychiatry from the University of Hull), for her input on the synthesis and summary of screening tools and neuropsychological assessments.

Funding

SP is funded by a PhD scholarship from the University of Hull. The funding source had no involvement in the study design, data collection, analysis or interpretation of the data, the writing of the report, or the decision to submit the article for publication.

References

1. Schofield P. Pain management in older adults. Medicine. 2017;45(1):41-5.
2. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. BMJ: British Medical Journal. 2015;350.
3. Brant JM. Assessment and management of cancer pain in older adults: Strategies for success. Asia-Pacific Journal of Oncology Nursing. 2018;5(3):248-53.
4. Santos FC, de Moraes NS, Pastore A, Cendoroglo MS. Chronic pain in long-lived elderly: prevalence, characteristics, measurements and correlation with serum vitamin D level. Revista Dor. 2015;16(3):171-5.
5. Presley CJ, Kapo J, Wang S, Canavan M, Sheinfeld E, Feder S, et al. Undertreated pain: Trends over time for older adults with and without cancer. Journal of Clinical Oncology. 2018;36(30_Suppl):15.
6. Lussier D, Gibson SJ. Prevalence and relevance of pain in older persons. Pain Medicine. 2012;13(Suppl_2):S23-6.
7. Rastogi R, Meek BD. Management of chronic pain in elderly, frail patients: Finding a suitable, personalized method of control. Clinical Interventions in Aging. 2013;8:37-46.
8. Tracy B, Morrison S. Pain Management in Older Adults. Clinical therapeutics. 2013;35(11):1659-68.
9. Hall T. Management of persistent pain in older people. Journal of Pharmacy Practice and Research. 2016;46(1):60-7.
10. Kumar A, Allcock N. Pain in older people: Reflections and experiences from an older person's perspective. London: Help the Aged; 2008.
11. Prostran M, Vujović KS, Vučković S, Medić B, Srebro D, Divac N, et al. Pharmacotherapy of pain in the older population: The place of opioids. Frontiers in aging neuroscience. 2016;8:1-7.
12. Greene Naples J, Gellad WF, Hanlon JT. Managing pain in older adults: The role of opioid analgesics. Clinics in Geriatric Medicine. 2016;32(4):725-35.
13. Papaleontiou M, Henderson CR, Jr., Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: A systematic review and meta-analysis. Journal of the American Geriatrics Society. 2010;58(7):1353-69.
14. Cordts GA, Christo PJ. Effective treatments for pain in the Older Patient. New York: Springer; 2018.
15. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. Annals of internal medicine. 2015;162(4):276-86.
16. Eccleston C, Fisher E, Thomas KH, Hearn L, Derry S, Stannard C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. 2017; Issue 11. Art. No: CD010323.
17. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long‐term opioid management for chronic noncancer pain. Cochrane Database of Systematic Reviews. 2010; Issue 1. Art. No: CD006605.
18. Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017; Issue 10. Art. No.: CD012509.
19. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105-20.
20. Chau DL, Walker V, Pai L, Cho LM. Opiates and elderly: Use and side effects. Clinical Interventions in Aging. 2008;3(2):273-8.
21. Rogers E, Mehta S, Shengelia R, Reid MC. Four strategies for managing opioid-induced side effects in older adults. Clinical Geriatrics. 2013;21(4):1-14.

22. Boland J, Boland E, Brooks D. Importance of the correct diagnosis of opioid-induced respiratory depression in adult cancer patients and titration of naloxone. Clinical Medicine. 2013;13(2):149-51.
23. Opioid Therapy in the 21st Century. 2nd ed. Smith HS, editor. New York: Oxford University Press; 2013.
24. Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: A good concept gone astray. BMJ: British Medical Journal. 2016;352.
25. Boland JW, Pockley AG. Influence of opioids on immune function in patients with cancer pain: From bench to bedside. British journal of pharmacology. 2018;175(14):2726-36.
26. Makris UE, Abrams RC, Gurland B, Reid M. Management of persistent pain in the older patient: A clinical review. JAMA. 2014;312(8):825-37.
27. Cantlay A, Glyn T, Barton N. Polypharmacy in the elderly. InnovAiT: Education and Inspiration for General Practice. 2016;9(2):69-77.
28. Akinbolade O, Husband A, Forrest S, Todd A. Deprescribing in advanced illness. Progress in Palliative Care. 2016;24(5):268-71.
29. Mordecai L, Reynolds C, Donaldson LJ, de C Williams AC. Patterns of regional variation of opioid prescribing in primary care in England: A retrospective observational study. British Journal of General Practice. 2018;68(668):e225-33.
30. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Therapeutic advances in drug safety. 2016;7(1):11-22.
31. Oh G, Abner EL, Fardo DW, Freeman PR, Moga DC. Patterns and predictors of chronic opioid use in older adults: A retrospective cohort study. PLOS ONE. 2019;14(1):e0210341.
32. Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. Journal of pain & palliative care pharmacotherapy. 2007;21(1):15-25.
33. Spitz A, Moore AA, Papaleontiou M, Granieri E, Turner BJ, Reid MC. Primary care providers' perspective on prescribing opioids to older adults with chronic non-cancer pain: A qualitative study. BMC geriatrics. 2011;11:35.
34. Højsted J, Kurita GP, Kendall S, Lundorff L, de Mattos Pimenta CA, Sjøgren P. Non-analgesic effects of opioids: the cognitive effects of opioids in chronic pain of malignant and non-malignant origin: An update. Current pharmaceutical design. 2012;18(37):6116-22.
35. Kendall SE, Sjøgren P, de Mattos Pimenta CA, Højsted J, Kurita GP. The cognitive effects of opioids in chronic non-cancer pain. Pain. 2010;150(2):225-30.
36. Kurita GP, Lundorff L, Pimenta CA, Sjøgren P. The cognitive effects of opioids in cancer: A systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2009;17(1):11-21.
37. Mailis-Gagnon A, Lakha SF, Furlan A, Nicholson K, Yegneswaran B, Sabatowski R. Systematic review of the quality and generalizability of studies on the effects of opioids on driving and cognitive/psychomotor performance. The Clinical journal of pain. 2012;28(6):542-55.
38. Ferreira DH, Boland JW, Phillips JL, Lam L, Currow DC. The impact of therapeutic opioid agonists on driving-related psychomotor skills assessed by a driving simulator or an on-road driving task: A systematic review. Palliative Medicine. 2018;32(4):786-803.
39. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesthesia & Analgesia. 2006;102(4):1255-66.
40. Gianni W, Ceci M, Bustacchini S, Corsonello A, Abbatecola AM, Brancati AM, et al. Opioids for the treatment of chronic non-cancer pain in older people. Drugs & Aging. 2009;26 (Suppl 1):63-73.
41. Moriarty O, Finn DP. Cognition and pain. Current Opinion Supportive Palliative Care. 2014;8(2):130-6.
42. Dhingra L, Ahmed E, Shin J, Scharaga E, Magun M. Cognitive Effects and Sedation. Pain Medicine. 2015;16(Suppl_1):S37-43.

43. Baldacchino A, Balfour DJ, Passetti F, Humphris G, Matthews K. Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. Neuroscience and biobehavioral reviews. 2012;36(9):2056-68.
44. Allegri N, Mennuni S, Rulli E, Vanacore N, Corli O, Floriani I, et al. Systematic review and meta-analysis on neuropsychological effects of long-term use of opioids in patients with chronic noncancer pain. Pain Practice. 2019;19(3):328-43.
45. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4(1):1.
46. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ: British Medical Journal. 2015;349.
47. Pask S, Dell'Olio M, Murtagh FEM, Boland J. A systematic review of how opioids affect cognition in older adults.: PROSPERO 2018: CRD42018092943; 2018 [Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=92943].
48. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. British Medical Journal. 2009;339:b2535.
49. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly". Geriatrics & Gerontology International. 2006;6(3):149-58.
50. World Health Organisation. Proposed working definition of an older person in Africa for the MDS Project. 2019 [Available from: http://www.who.int/healthinfo/survey/ageingdefnolder/en/.
51. Kmet LM, Cook LS, Lee RC. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. Alberta, Canada: Alberta Heritage Foundation for Medical Research; 2004.
52. Lee L, Packer TL, Tang SH, Girdler S. Self-management education programs for age-related macular degeneration: A systematic review. Australasian Journal on Ageing. 2008;27(4):170-6.
53. Maharaj S, Harding R. The needs, models of care, interventions and outcomes of palliative care in the Caribbean: a systematic review of the evidence. BMC palliative care. 2016;15:9.
54. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews: A product from the ESRC Methods Programme. 2006.
55. Corsinovi L, Martinelli E, Fonte G, Astengo M, Sona A, Gatti A, et al. Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain. Archives of Gerontology & Geriatrics. 2009;49(3):378-82.
56. Kamboj SK, Tookman A, Jones L, Curran HV. The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. Pain. 2005;117(3):388-95.
57. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2002;59(7):1015-21.
58. Gianni W, Madaio AR, Ceci M, Benincasa E, Conati G, Franchi F, et al. Transdermal buprenorphine for the treatment of chronic noncancer pain in the oldest old. Journal of Pain & Symptom Management. 2011;41(4):707-14.
59. Guerriero F, Roberto A, Greco MT, Sgarlata C, Rollone M, Corli O. Long-term efficacy and safety of oxycodone-naloxone prolonged release in geriatric patients with moderate-to-severe chronic noncancer pain: a 52-week open-label extension phase study. Drug design, development & therapy. 2016;10:1515-23.
60. Puustinen J, Nurminen J, Lopponen M, Vahlberg T, Isoaho R, Raiha I, et al. Use of CNS medications and cognitive decline in the aged: a longitudinal population-based study. BMC Geriatrics. 2011;11:70.

61. Karp JF, Reynolds CF, 3rd, Butters MA, Dew MA, Mazumdar S, Begley AE, et al. The relationship between pain and mental flexibility in older adult pain clinic patients. Pain Medicine. 2006;7(5):444-52.
62. Pappagallo M, Raja SN, Haythornthwaite JA. Oral opioids in the management of postherpetic neuralgia: A prospective survey. Analgesia. 1994;1:51-5.
63. McNamara P. Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care. Palliative Medicine. 2002;16(5):425-34.
64. Clemons M, Regnard C, Appleton T. Alertness, cognition and morphine in patients with advanced cancer. Cancer Treatment Reviews. 1996;22(6):451-68.
65. Wesnes KA, McKeith IG, Ferrara R, Emre M, Del Ser T, Spano PF, et al. Effects of rivastigmine on cognitive function in dementia with lewy bodies: a randomised placebo-controlled international study using the cognitive drug research computerised assessment system. Dementia and geriatric cognitive disorders. 2002;13(3):183-92.
66. Musich S, Wang SS, Slindee L, Kraemer S, Yeh CS. Prevalence and characteristics associated with high dose opioid users among older adults. Geriatric Nursing. 2019;40(1):31-6.
67. Faculty of Pain Medicine. Opioids aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. 2019 [Available from: https://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware.
68. Bruera E, Franco JJ, Maltoni M, Watanabe S, Suarez-Almazor M. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. Journal of Pain & Symptom Management. 1995;10(4):287-91.
69. Hunt R, Fazekas B, Thorne D, Brooksbank M. A comparison of subcutaneous morphine and fentanyl in hospice cancer patients. Journal of Pain & Symptom Management. 1999;18(2):111-19.
70. Kurita GP, Sjogren P, Ekholm O, Kaasa S, Loge JH, Poviloniene I, et al. Prevalence and predictors of cognitive dysfunction in opioid-treated patients with cancer: a multinational study. Journal of Clinical Oncology. 2011;29(10):1297-303.
71. Kurita GP, Lundorff L, Pimenta CA, Sjogren P. The cognitive effects of opioids in cancer: a systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2009;17(1):11-21.
72. Gupta U, Verma M. Placebo in clinical trials. Perspectives in clinical research. 2013;4(1):49-52.
73. Bhide A, Shah PS, Acharya G. A simplified guide to randomized controlled trials. Acta Obstetricia et Gynecologica Scandinavica. 2018;97(4):380-7.
74. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: A review of clinical and preclinical research. Progress in Neurobiology. 2011;93(3):385-404.
75. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: A narrative review. Expert Opinion on Drug Safety. 2018;17(12):1185-96.
76. Rawle MJ, Cooper R, Kuh D, Richards M. Associations Between Polypharmacy and Cognitive and Physical Capability: A British Birth Cohort Study. Journal of the American Geriatrics Society. 2018;66(5):916-23.
77. Wright RM, Roumani YF, Boudreau R, Newman AB, Ruby CM, Studenski SA, et al. Impact of Central Nervous System (CNS) medication use on cognition decline in community dwelling older adults: Findings from the health, aging and body composition study. Journal of the American Geriatrics Society. 2009;57(2):243-50.
78. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State - Practical Method for Grading Cognitive State of Patients for Clinician. Journal of Psychiatric Research. 1975;12(3):189-98.
79. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: An update. International journal of geriatric psychiatry. 2010;25(2):111-20.

80. Breton A, Casey D, Arnaoutoglou NA. Cognitive tests for the detection of mild cognitive impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies. International journal of geriatric psychiatry. 2019;34(2):233-42.
81. Christa MSB, Minett T, Pagett E, Siervo M, Brayne C, McKeith IG. Diagnosing Mild Cognitive Impairment (MCI) in clinical trials: A systematic review. BMJ Open. 2013;3(2).
82. Mitchell A. The Mini-Mental State Examination (MMSE): Update on Its Diagnostic Accuracy and Clinical Utility for Cognitive Disorders. In: Larner AJ, editor. Cognitive Screening Instruments: A Practical Approach. 2nd ed. Switzerland: Springer; 2016. p. 37-48.
83. Newman JC, Feldman R. Copyright and Open Access at the Bedside. New England Journal of Medicine. 2011;365(26):2447-9.
84. Boland JW, Allgar V, Boland EG, Oviasu O, Agar M, Currow DC, et al. Effect of Opioids and Benzodiazepines on Clinical Outcomes in Patients Receiving Palliative Care: An Exploratory Analysis. Journal of Palliative Medicine. 2017;20(11):1274-9.
85. Ciesielska N, Sokolowski R, Mazur E, Podhorecka M, Polak-Szabela A, Kedziora-Kornatowska K. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. Psychiatria polska. 2016;50(5):1039-52.
86. Clarnette R, O'Caoimh R, Antony DN, Svendrovski A, Molloy DW. Comparison of the Quick Mild Cognitive Impairment (Qmci) screen to the Montreal Cognitive Assessment (MoCA) in an Australian geriatrics clinic. International journal of geriatric psychiatry. 2017;32(6):643-9.
87. Ridley N, Batchelor J, Draper B, Demirkol A, Lintzeris N, Withall A. Cognitive screening in substance users: Diagnostic accuracies of the Mini-Mental State Examination, Addenbrooke's Cognitive Examination–Revised, and Montreal Cognitive Assessment. Journal of Clinical and Experimental Neuropsychology. 2018;40(2):107-22.
88. Copersino ML, Schretlen DJ, Fitzmaurice GM, Lukas SE, Faberman J, Sokoloff J, et al. Effects of Cognitive Impairment on Substance Abuse Treatment Attendance: Predictive Validation of a Brief Cognitive Screening Measure. The American journal of drug and alcohol abuse. 2012;38(3):246-50.
89. Copersino ML, Fals-Stewart W, Fitzmaurice G, Schretlen DJ, Sokoloff J, Weiss RD. Rapid cognitive screening of patients with substance use disorders. Experimental and Clinincal Psychopharmacology. 2009;17(5):337-44.
90. Ersek M, Cherrier MM, Overman SS, Irving GA. The cognitive effects of opioids. Pain Management Nursing. 2004;5(2):75-93.
91. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. QJM: An International Journal of Medicine. 2007;100(8):469-84.
92. Chaytor N, Schmitter-Edgecombe M. The Ecological Validity of Neuropsychological Tests: A Review of the Literature on Everyday Cognitive Skills. Neuropsychology review. 2003;13(4):181-97.
93. Goldberg TE, Harvey PD, Wesnes KA, Snyder PJ, Schneider LS. Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials. Alzheimer's & Dementia. 2015;1(1):103-11.
94. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. Journal of neurology, neurosurgery, and psychiatry. 2007;78(8):790-99.
95. Whelihan WM, DiCarlo MA, Paul RH. The relationship of neuropsychological functioning to driving competence in older persons with early cognitive decline. Archives of Clinical Neuropsychology. 2005;20(2):217-28.
96. Apolinario D, Magaldi RM, Busse AL, Lopes LC, Kasai JYT, Satomi E. Cognitive impairment and driving: A review of the literature. Dement Neuropsychol. 2009;3(4):283-90.
97. Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. British journal of clinical pharmacology. 2013;75(1):60-78.
98. Sivanesan E, Gitlin MC, Candiotti KA. Opioid-induced Hallucinations: A Review of the Literature, Pathophysiology, Diagnosis, and Treatment. Anesthesia & Analgesia. 2016;123(4):836-43.

99. Jamison RN, Dorado K, Mei A, Edwards RR, Martel MO. Influence of opioid-related side effects on disability, mood, and opioid misuse risk among patients with chronic pain in primary care. Pain Reports. 2017;2(2):e589.
100. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. Pharmacy Practice. 2014;12(4):489-89.
101. Curran HV, Kleckham J, Bearn J, Strang J, Wanigaratne S. Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose-response study. Psychopharmacology. 2001;154(2):153-60.
102. Hanks GW, O'Neill WM, Simpson P, Wesnes K. The cognitive and psychomotor effects of opioid analgesics. II. A randomized controlled trial of single doses of morphine, lorazepam and placebo in healthy subjects. European journal of clinical pharmacology. 1995;48(6):455-60.

Appendix 1 Example of the full search strategy

Example of Ovid MEDLINE(R) Epub ahead of print, in-process & other non-indexed citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present search strategy:

1. exp Analgesic, Opioid/
   [Drug Terms (Non MeSH)]
   - Alfentanil
   - Alphaprodine
   - Buprenorphine
   - Buprenorphine, Naloxone Drug Combination
   - Butorphanol
   - Codeine
   - Dextromoramide
   - Dextropropoxyphene
   - Dihydromorphine
   - Diphenoxylate
   - Enkephalin, Ala(2)-MePhe(4)-Gly(5)-
   - Enkephalin, D-Penicillamine (2,5)-
   - Ethylketocyclazocine
   - Ethylmorphine
   - Etorphine
   - Fentanyl
   - Heroin
   - Hydrocodone
   - Hydromorphone
   - Levorphanol
   - Meperidine
   - Meptazinol
   - Methadone
   - Methadyl Acetate
   - Morphine
   - Nalbuphine
   - Opiate Alkaloids
   - Opium
   - Oxycodone
   - Oxymorphone
   - Pentazocine
   - Phenazocine
   - Phenoperidine
   - Pirinitramide
   - Promedol
   - Sufentanil
   - Tapentadol
   - Tilidine
   - Tramadol
2. Dezocine.mp

3. Dihydrocodeine.mp
4. Opiate*.mp
5. Opioid*.mp
6. Propoxyphene.mp
7. Tapentadol.mp
8. Trimeperidine.mp
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. exp Cognitive Dysfunction/
11. cognit*.mp
12. 10 OR 11
13. exp Aged/
    Aged, 80 and over
    Frail elderly
14. Elder*.mp
15. Geriatr*.mp
16. Old* adult*.mp
17. Old* age*.mp
18. Old* Generation*.mp
19. Old* people*.mp
20. Senior*.mp
21. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. 9 AND 12 AND 21

Table 1. Inclusion and exclusion criteria

Study characteristic	Include	Exclude
Participants	Older adults aged ≥65 with cancer and/or chronic non-cancer pain (including an overall mean age of ≥65, a mixed population with at least 50% aged ≥65 or a clear subgroup analysis reporting on participants aged ≥65)	Populations where substance misuse, psychiatric illnesses, neurocognitive/neurodegenerative diseases (e.g. Alzheimer's) and brain injury are present or studies that only consider healthy older adults.
Exposure and assessment	Studies exploring opioid use where screening tools and/or neuropsychological assessments have been used to detect opioid-induced cognitive impairment.	Studies that consider recreational use and perioperative use of opioids, that aim to block the effects of opioids or that use opioids for antitussive relief, diarrhoea or use opioids not used within clinical practice.
	Studies exploring multiple medications effects on cognition, as long as opioids were included and a clear subgroup analysis was available.	Studies that use self-report assessment or a healthcare professional opinion of cognitive function.
Study design and publication type	Randomised controlled trials, quasi-experimental studies and observational studies, which had been published in peer-review or grey literature.	Case reports, reviews or systematic literature reviews, qualitative studies, opinion pieces, editorials, comments, news and letters.
Publication date, setting (including country or care setting) or language	Any	

Table 2. Summary of studies

Study	Design	Participants recruited; including diagnosis and age (mean age, range and/or % of ≥65)	Setting	Opioid type and oral morphine equivalent daily dose (MEDD; range)	Tools and assessments	Quality score
1. Clemons et al. (1996) *UK*	Quasi-experimental	29 participants (64.5; 51.7% aged ≥65); Group 1**:** 16 healthy participants (65.4), Group 2: 6 advanced cancer patients not taking opioids (62.8) and Group 3: 7 advanced cancer patients taking opioids (61)	Hospice (Inpatient/ outpatient)	Controlled release morphine sulphate or morphine sulphate solution 104.3mg (50 – 200mg)	GRT, LMT, NART, RT, SCWT	Adequate (0.55)
2. Corsinovi et al. (2009) *Italy*	Randomized, single blind, controlled	154 participants with persistent osteoarthritis-related pain; Group 1: 52 participants taking Oxycodone (79.2), Group 2: 52 participants taking Codeine (77.1), Group 3: 50 participants on conventional therapy (77.1)	Nursing home	Immediate release oxycodone 32mg* Immediate release codeine 11.5mg*	MMSE	Strong (0.93)
3. Gianni et al. (2011) *Italy*	Observational (Prospective cohort)	93 participants with osteoarthritis-related pain (79.1)	Multicentre (Ambulatory)	Buprenorphine 60 – 95mg	MMSE	Good (0.77)
4. Guerriero (2016) *Italy*	Observational (Longitudinal prospective cohort)	60 participants with moderate to severe chronic non-cancer pain (81.7)	Rehabilitation centre	Prolonged-release oxycodone 34.8mg*	MMSE	Strong (0.91)
5. Kamboj et al. (2005) *UK*	Double-blind, placebo-controlled, cross-over	14 participants; 12 (85.7%) with cancer pain and 2 (14.3%) with chronic back pain (65.2)	Palliative care unit (Inpatient/ Outpatient)	Sustained release opioid 190.7mg (30 – 800mg) Immediate release morphine 21.4mg (5-100mg)	PR, VFT, TMT, FT, DS, MST, TST, EC, ECD	Strong (0.82)
6. Karp et al. (2006)	Observational (Cross-sectional survey)	57 participants with non-cancer diagnoses (76.1) Opioid use present in 27 participants	Older adult pain management program	Not reported	MMSE, D-KEFS TMT, DSST, ILT	Adequate (0.55)

Table 2. Summary of studies continued

Study	Design	Sample; including diagnosis and age (mean age, range or % or ≥65)	Setting	Opioid type and oral morphine equivalent daily dose (MEDD; range)	Tools and assessments	Quality score
7. McNamara et al. (2002) *UK*	Observational (Single-centre, non-comparative, open label)	19 participants with cancer pain (65.7)	Hospice	Fentanyl 120mg (60 – 1080mg)	CDR	Good (0.73)
8. Pappagallo et al. (1994) *USA*	Observational (Longitudinal survey)	20 participants with postherpetic neuralgia (72.2)	Pain treatment centre	Slow release morphine 47.1mg (15 – 90mg) Compounded slow release oxycodone 55mg (15 – 90mg) Hydomorphone 64mg Methadone 100mg Overall MEDD dose 54.4mg	MMSE	Adequate (0.68)
9. Puustinen et al. (2011) *Finland*	Observational (Longitudinal population-based)	565 participants, including cancer and non-cancer diagnoses (70.5) Opioid use present at baseline (N= 9), follow-up (N= 43) and at both time-points (N= 3). Opioid users had arthritic diseases.	Municipality of Lieto	Codeine, dextropropoxyphene, ethylmorphine and dextromethorphan. Dose not taken into account.	MMSE	Strong (0.86)
10. Raja et al. (2002) *USA*	Double-blind, placebo-controlled, crossover	76 participants with postherpetic neuralgia (71)	Referrals and advertisements (Centre not clearly acknowledged)	Controlled-release morphine 91mg (15 – 225mg) Methadone (alternative to morphine) 150mg	MMSE, GPT, HVLT, SST	Strong (0.93)

CDR: Cognitive Drug Research (CDR) computerised assessment, D-KEFS TMT: Delis-Kaplan Executive Trail Making Test, DS: Digit Span Test, DSST: Digit Symbol Subtest, EC: Elevator Counting, ECD: Elevator Counting with Distraction, FT: Finger Tapping Test, GPT: Grooved Pegboard Task, GRT: Grammatical Reading Test, HVLT: Hopkins Verbal Learning Test, ILT: Incidental learning tests, LMT: Logical Memory Test, MMSE: Mini-Mental State Exam, MST: Map Search Test, NART: National Adult Reading Test, PR: Prose Recall, RT: Reaction Time, SCWT: Stroop Colour-Word Test, SST: Symbol Substitution Task (Wechsler Adult Intelligence Test – Revised), TMT: Trail Making Task, TST: Telephone Search Test, VFT: Verbal Fluency Test

*Opioid combined with acetaminophen (Corsinovi et al. 2009) and naloxone (Guerriero et al. 2016).

Table 3. Summary of cognitive tests used in each study, cognitive domains assessed and outcomes of tests

Study	Timing of test	Assessments and tools used	Description provided by authors	Cognitive domain	Outcomes and comparison between groups
Clemons et al. (1996)	Tests completed 1.5h after oral morphine and 4h after controlled release opioid between mid-morning and mid-afternoon. Tests were completed at a similar time across all visits from baseline to a maximum of 23 days. Visits varied per participant	**Grammatical Reading Test**	The test consists of 64 sentences with varying levels of complexity. The test has been proven to be sensitive to drug effects. The participant is provided with a demonstration card, which had a written statement with the answer. Multiple practice cards (without the same answer) were then shown and the participant was asked to determine whether the statement was true or false. The series of cards were presented within 3-minutes. Scores were calculated using the mean time to answer each item and the percentage of errors. A different sequence of cards was used at each test.	Concentration and reasoning	No difference in the percentage of errors between cancer groups*
		Logical Memory Test *(Sub-test of Wechsler Memory Scale)*	A fictitious news event (58 – 64 words in length) was presented to participants. Participants are asked to recall the news event. Each story is divided into 21 details; with one point awarded for each detail recalled word perfect or an exact synonym. Half points are awarded for a close approximation. Different passages were used at each test session.	Everyday memory (Including short- and long-term memory)	No difference in memory score and mean time per item between cancer groups* *Authors did acknowledge that morphine group took slightly more time per item*
		National Adult Reading Test	A word-reading test to test participants' capability of pronouncing 50 phonetically irregular words. The total number of errors is then tabulated. The authors acknowledge that the test is resistant to drug effects.	Pre-morbid IQ	No difference in mean IQ scores between cancer groups*

		Reaction Time	This test determines the effect of opioids on the mean reaction time by reducing concentration. Reduced concentration would result in varied response times and would increase the standard deviation of scores. This would contrast with participants who have 'full' concentration, since their response times should be narrower in range and have a reduced standard deviation. After each session, the standard deviation of all response times during that session was calculated.	Reaction speed and concentration	No difference in reaction speed between cancer groups*
		Stroop-colour-word Test	This test measures the time taken for participants to read a colour word when printed with incongruent ink (e.g. the word 'Green' printed in red). The correct response is to say the colour of the word instead of reading the word. A practice session of 20 items was conducted, followed by the test. The total time taken and number of errors was recorded.	Selective attention and cognitive flexibility	No difference in performance on word, colour or colour-word cards between cancer groups* *Authors acknowledge that morphine group had slightly diminished performance on colour-card*
Corsinovi et al. (2009)	Baseline and at 6-months. No other details provided	**MMSE**	Cognitive status was assessed using the MMSE: lower scores were an indication of cognitive impairment.	Cognitive function, including: attention, language, memory and orientation	No difference in cognitive function; GLM between groups F= 0.1, p<0.877. GLM within groups F= 1.3, p<0.28
Gianni et al. (2011)	Baseline and at follow-ups (7, 14, 30, 60 and 90 days)	**MMSE**	MMSE was used to evaluate cognitive impairment, whilst adjusted for age and education.	Cognitive function, including: attention, language, memory and orientation	No difference in cognitive function*

Guerriero et al. (2016)	Baseline and week 52	**MMSE**	Cognitive state was assessed with normal cognition being scored as >25.	Cognitive function, including: attention, language, memory and orientation	No difference in cognitive function*
Kamboj et al. (2005)	Pre-treatment and post-treatment (45 minutes after treatment)	**Digit Span**	Participants forwards and backwards digit span was assessed in a standard format.	Attention and working memory	No difference between forward digit span (Placebo: 6.2±1.2 and Morphine 6.0±0.8) in forward digit span or backward digit span (Placebo: 3.6±1.1 and Morphine: 4.0±1.0)
		Finger Tapping	Participants were asked to press a computer keyboard space bar with their dominant hand using their index finger as quickly as possible for 1 minute. The score was the number of taps recorded.	Psychomotor sedation	No difference in tapping rate between placebo (267.1 ± 44.6) and following morphine (260 ± 38.5)
		Prose Recall (Rivermead Behavioural Memory Test) .	Four versions of the prose recall were used. Participants listened to a news story (prose passage) and were asked to recall the passage immediately, pre- and post-treatment. Later in the post-treatment session, participants were asked for delayed recall of the news stories from pre-treatment and post-treatment. The delay between immediate and delayed recall was 65 minutes for the pre-treatment story and 20 minutes for the post-treatment story. Standard scoring was used, with 1 point for every correctly recalled 'idea unit' or exact synonym. Half points were awarded for partial recall or synonym. Previous research demonstrated sensitivity to opioid-induced recall impairments (101).	Immediate and delayed episodic memory	Decline in immediate recall following morphine but no main effect of treatment ($F(1,13)=4.366$, $P=0.057$) Decline in delayed recall for prose passages before and after morphine, significant main effect of treatment ($F(1, 13)=13.18$, $P=0.003$) Individual comparisons showed morphine impaired recall post-treatment; 6.6±2.9 idea

				units recalled after placebo and 4.2±2.8 after morphine ($F(1,13)=13.01$, $P=0.003$ Recall of pre-treatment story was reduced following morphine (4.7±2.0 idea units) compared to placebo 6.1±2.5 idea units ($F(1,13)= 6.53$, $P = 0.024$)
	Trail Making Test	A timed tracking task that consists of two parts. Part A comprises of joining numbered circles (1-25) and Part B requires participants to join alternating numbers (1-13) and alphabetised circles (A-L). Mistakes would be highlighted to participants but the timing would be continuous. Sample sheets were provided for both parts to ensure that the participant understood the task. A difference score is produced by subtracting A from B, which produces a score that highly correlates with mental ability tests.	Attention, psychomotor speed and cognitive flexibility (Part A & B: psychomotor performance, Part B: attention and B-A: cognitive flexibility)	Improved performance on part A following morphine compared with placebo (Z=2.13, P=0.033). On part B those on morphine were slower (Z= 2.12, P= 0.034). Set shifting and conceptual flexibility (time to complete trails B – trails A) was increased following morphine (Z= 2.28, P= 0.023
	Verbal Fluency	Participants were asked to generate as many words as possible in one minute with a particular letter (e.g. B or M) to assess phonemic fluency, avoiding proper nouns and inflections of the same word. Semantic	Phonemic fluency and semantic fluency (Cognitive flexibility)	No significant effects of treatment for phonemic fluency (10.1±5.0 words following placebo; 9.5±3.3 following morphine) or semantic

	fluency was assessed using categories of fruit and vegetables.		fluency (10.6±4.7 words following placebo; 9.5 following morphine)
Tests of Everyday Attention			
Elevator Counting	Participants are asked to imagine themselves in an elevator where they do not have a visual floor-indicator. They were asked to count tones (played on a tape recorder) to determine which floor they would be on. Seven sets of tone sequences were to be counted, varying from three to fourteen tones within one series. A score of 7 (one point per series correctly counted) indicated a 'normal' performance, whereas 6 indicated 'possible abnormality' and 5 indicates 'abnormality'.	Auditory sustained attention	No difference in performance between placebo (6.5±0.5) and morphine (6.2±1.0)
Elevator Counting with Distraction	This task requires participants to count low frequency tones while ignoring high frequency tones. A series of low and high frequency tones containing between two and fourteen target low tones is played. Participants are awarded a point for each series when the correct number of low tones was counted.	Auditory selective attention	No difference in performance between placebo (7.2±2.5) and morphine (9.3±8.2) groups
Map Search	A time-limited task that requires participants to search for and mark symbols on a map of Philadelphia within two minutes.	Selective visual attention	No difference between placebo (37.6±16.9) and morphine (36.9±14.8) in number of symbols correctly identified
Telephone Search	This is a timed visual task. Participants are asked to imagine that they are in Philadelphia and need to find a plumber or a restaurant. They are asked to scan the 'yellow pages' directory for plumbers or	Selective attention	No difference between placebo (4.8±1.0) and morphine (5.1±1.4) in time per target

			restaurants and place a mark on entries that had the same symbols (e.g. two stars or two circles). Participants are asked to work as quickly and accurately as possible and to not check their responses. The time taken to complete the search and number of correctly marked targets are recorded (false positives were ignored). The number of targets divided by the time taken to complete the task to create the dependent variable (time per target).		
Karp et al. (2006)	Not reported	**MMSE**	Cognitive function was assessed to determine participant eligibility. All subjects were required to have a Mini Mental State Exam score of ≥ 24 to participate.	N/A	N/A
		Delis-Kaplan Executive Function System Trail Making Test	Mental flexibility was assessed with the Trail Making Test of the Delis-Kaplan Executive Function System (D-KEFS). This test is similar to the traditional Trail Making Test, but is comprised of five subtests that may be used to correct for processes other than mental flexibility that may be contributing to a slow response time or to set-shifting errors. These tests are also age-adjusted. The D-KEFS Trail Making subtests administered to patients include the number-letter switching condition (similar to the traditional Trails B) that is a measure of mental flexibility. The other is a test of motor speed (similar to the traditional Trails A).	Mental flexibility (cognitive flexibility) and psychomotor speed	No difference between opioid users (7.7±3.9) and non-opioid users (9.3±4.4) in mental flexibility (number-letter switching), t=1.38, df= 50, p= 0.17 No difference between opioid users (9.9±3.5) and non-opioid users (10.7±3.4) in psychomotor speed, t= 0.81, df= 50, p= 0.42 Reduced number (26 opioid users/26 non-opioid users)

	Digit Symbol Subtest (Wechsler Adult Intelligence Scales – Revised)	Highly sensitive to neuropsychological dysfunction (31) and is another probe of mental flexibility. This visuoperceptual decoding task requires the subject to associate single-digit numbers with unfamiliar symbols. A stimulus set of nine printed digit-symbol pairs is presented above rows of numbers without the appropriate symbols. The subject is instructed to draw the correct symbol below each of the numbers using the digit-symbol code presented above. The score is based on the number of substitutions completed within 90-seconds.	Cognitive flexibility (referred to as mental flexibility)	No difference between opioid users (10.9±3.0) and non-opioid users (11.7±2.8), t=0.91, df=49, p= 0.37 Reduced number (25 opioid users/26 non-opioid users)
	Incidental Learning Tests	Memory was assessed with the incidental learning tests administered immediately following the DSST. Paired-recall involves completing a number of Digit Symbol items without access to the code key; free recall, simply reproducing the symbols from memory. These tests of memory were only administered if patients completed four rows of the DSST test within 120 seconds. The reason for this was to standardize the time each patient was exposed to the digit/symbol stimuli.	Memory (including free recall and paired recall	Unprompted memory was worse in opioid users (6.3±1.1) compared to non-opioid users (7.0±1.1) in the free recall test, t= 2.17, df= 39, p=0.04 No difference in paired recall between the opioid users (6.9±4.2) and non-opioid users (7.7±5.1), t= 0.56, df= 39, p= 0.58 Reduced number (20 opioid users/21 non-opioid users)

McNamara et al. (2002)	Baseline and Day 14 (last recorded assessment - used as the last value when data were missing – 'Last value carried forward')	**Cognitive Drug Research (CDR) computerised assessment**	A series of tests were used, including: simple reaction time, choice reaction time, digit vigilance, memory scanning, immediate and delayed word recall, word recognition, picture recognition and critical flicker fusion threshold. Tasks are presented on a microcomputer and participants responded using one of two buttons within a single box. For a further breakdown on tests, see Hanks et al. (1995) (102).	Power of Concentration *(Ability to attend to change or concentrate for sustained periods of time)*	No significant difference between baseline (1654 (1484, 1825)) and last recorded visit in ability to concentrate (1623 (1469, 1776), P= 0.6771)
				Quality of concentration *(Accuracy and speed of concentration, combined)*	No significant difference between baseline (89.3 (86.8, 91.7)) and last recorded visit in accuracy and speed of concentration (89.2 (85.6, 92.9), *P*= 0.8341)
				Quality of working memory *(Ability to retain and retrieve information in short-term memory)*	Significant improvement in quality of working memory between baseline (1.5 (1.3, 1.8)) and last recorded visit (1.7 (1.6, 1.8), *P*= 0.0345)
				Quality of secondary memory *(Ability to retain and retrieve information in long-term memory)*	No significant difference between baseline (207 (188, 226)) and last recorded visit in ability to retrieve information from long-term memory (192 (167, 217), *P*= 0.3218)
				Speed of memory *(Speed of information retrieval)*	Significant improvement in speed of memory from baseline (5551 (4583, 6519)) and last recorded visit 4878 (4246, 5511), *P*= 0.0212)

Pappagallo et al. (1994)	Baseline and 2-months	**MMSE**	Cognition was assessed using the Mini-Mental Status Exam.	Cognitive function, including: attention, language, memory and orientation	No difference in cognition at 2-month follow-up (29.9±0.1, N=20, *P*=0.6)
Puustinen et al. (2011)	Measured at both phase 1 and phase 2	**MMSE**	The test comprises of 23-items, and the sum of scores ranges from 0 to 30. Higher scores indicate better cognitive performance. The mean change in MMSE sum scores during follow-up was used as an outcome variable.	Cognitive function, including: attention, language, memory and orientation	MMSE scores of opioid users were significantly worse than the group (no medications with effects to CNS) (*P*= 0.032) MMSE scores of opioid users were significantly worse than the control group (non-users of corresponding medications) (*P*= 0.021) The combination of opioids and other CNS medications was also associated with cognitive decline (*P*= 0.007)
Raja et al. (2002)	Baseline and maintenance. Each treatment period lasted 8 weeks (with titration, maintenance and taper phase), with 3 treatment periods (opioid,	**MMSE**	Cognitive function was assessed to determine participant eligibility.	N/A	N/A
		Grooved Pegboard Task	No description provided.	Concentration and psychomotor function	No difference in performance* *Practice effects observed*
		Hopkins Verbal Learning Test	The test comprises a 12-item word list, which is composed of four words from three semantic categories. Participants read the word list and aim to memorise the words. The word list is then read to the participant at a rate of 2 seconds per word.	Verbal learning and memory	No difference in performance*

.	tricyclic antidepressants and placebo). Treatment periods were separated by a week without drugs		The participant's free recall of the list is recorded. This is repeated for two more trials. At the end of the third trial, the participant is read 24 words and is asked comment 'yes' for words that appeared on the recall list (12 targets) and 'no' for words that did no (12 distractors). Half of the distractors are from the same semantic category as the targets (related distractors), whilst half are drawn from other categories (unrelated distractors). There are 6 forms of the test and requires no more than 10 minutes to administer.		
		Symbol Substitution Task (Wechsler Adult Intelligence Test – Revised)	No description provided.	Manual dexterity and psychomotor speed	No difference in performance*

GLM: General Linear Model, MMSE: Mini-Mental State Exam

* Clemons et al. (1996): Statistical significance between advanced cancer groups was not reported, inferences based on author description and mean trends. Gianni et al. (2011): P value not provided but authors note the outcome is not statistically significant. Guerriero et al. (2016): Statistical significance is not reported but mean MMSE score from baseline to endpoint provided in graph, authors acknowledge MMSE score remained stable across time-points. Raja et al. (2002): P values not provided but authors noted that treatment did not influence performance on any measure. Authors presented means and standard deviations.

Table 4. A summary of opioids used across included studies and oral morphine equivalent conversion

Study	Opioid type, route of administration and length of use	Reported opioid dose (Mean dose and/or range)	Oral morphine equivalent daily dose (MEDD; Mean and/or range)	Average MEDD (Mean and/or range)
Clemons et al. (1999)	**Type:** Controlled-release morphine sulphate or morphine sulphate solution **Route**: Oral **Length of use:** No exact date of commencement for 5/7 participants. Earliest known date was used; approximately 3 – 72 weeks.	104.3mg/d (50 – 200mg)	104.3mg (50 – 200mg)	104.3mg (50 – 200mg)
Corsinovi et al. (2009)	**Type:** Immediate release oral oxycodone **Route:** Oral **Length of use:** 6 weeks	Baseline: 5mg/12h Average daily dose: 10 – 20mg/d Average dose at end of study: 16mg/d	Baseline: 20mg Average daily dose: 20 – 40mg Average dose at end of study: 32mg	32mg
	Type: Immediate release codeine **Route:** Oral **Length of use:** 6 weeks	Baseline: 30mg/8h Average daily dose: 90 – 120mg/d Average dose at end of study: 115mg/d	Baseline: 9mg Average daily dose: 9 – 12mg Average dose at end of the study: 11.5mg	11.5mg
Gianni et al. (2011)	**Type:** Buprenorphine **Route:** Transdermal **Length of use:** 3 months	End of 3-month observation 11.7 µg/h in 3.5%; 17.5 µg/h in 11.6%; 35 µg/h in 74.4%; 52.5 µg/h in 9.3%; 70 µg/h in 1.2%.	End of 3-month observation 20 – 31.7mg/d in 3.5% 30 – 47.5mg/d in 11.6% 60 – 95mg/d in 74.4% 95 – 145mg/d in 9.3% 125 – 190mg/d in 1.2%	60 - 95mg

Study	Opioid type, route of administration and length of use	Reported opioid dose (Mean dose and/or range)	Oral morphine equivalent daily dose (MEDD; Mean and/or range)	Average MEDD (Mean and/or range)
Guerriero et al. (2016)	**Type:** Oxycodone prolonged release **Route:** Oral **Length of use:** 52 weeks	Baseline: 10mg/d Week 4: 14.4mg/d ± 4.9mg/d Week 52: 17.4mg/d ± 7.7mg/d During follow-up, the daily dose increased to 20mg/d in 42% of patients at 4 weeks and to 40mg/d at 52 weeks in only 6% of patients.	Baseline: 20mg Week 4: 28.8mg ± 9.8mg Week 52: 34.8mg ± 15.4mg During follow-up, the daily dose increased to 40mg/d in 42% of patients at 4 weeks and to 80mg/d at 52 weeks in only 6% of patients.	34.8mg ± 15.4mg
Kamboj et al. (2005)	**Type:** Sustained release morphine **Route:** Oral (50%), transdermal patch (42.9%) and syringe driver (7.1%) **Length of use:** 11.7 days (SD: 4.7 days)	190.7mg/d ± 266.6 mg/d (30–800 mg/d)	190.7mg ± 266.6 mg (30 – 800 mg)	190.7mg ± 266.6 mg (30 – 800 mg)
	Type: Immediate release morphine **Route:** Oral **Length of use: Mean:** 11.7 days (SD: 4.7 days)	21.4mg/d ± 25.6mg/d (5 – 100mg/d)	21.4mg ± 25.6mg (5 – 100mg)	21.4mg ± 25.6mg (5 – 100mg)
Karp et al. (2006)	Not reported	Not reported	Not reported	Not reported
McNamara et al. (2002)	**Type:** Fentanyl **Route:** Transdermal **Length of use:** 14 days	Baseline: 25µg/h or 50µg/h Maintenance dose of 50µg/h – 100µg/h (25µg/h – 450µg/h).	Baseline 60mg – 90mg or 120mg – 190mg Maintenance dose of 120mg – 240mg (60mg – 1080mg)	120mg – 240mg (60mg – 1080mg)

Study	Opioid type, route of administration and length of use	Reported opioid dose (Mean dose and/or range)	Oral morphine equivalent daily dose (MEDD; Mean and/or range)	Average MEDD (Mean and/or range)
Pappagallo et al. (1994)	**Type:** Slow release morphine **Route:** Oral **Length of use:** Mean: 11.86 months (3 – 20 months)	47.1mg/d (15mg/d - 90mg/d)	47.1mg (15mg – 90mg)	54.5mg
	Type: Compounded slow release oxycodone **Route:** Oral **Length of use:** Mean: 7 months	27.5mg/d (7.5mg/d – 45mg/d)	55mg (15mg – 90mg)	
	Type: Hydromorphone **Route:** Oral **Length of use:** Mean: 21 months	16mg/d	64mg	
	Type: Methadone **Route:** Oral **Length of use:** Mean: 7 months (Range: 2-12)	10mg/d	100mg	
Puustinen et al. (2011)	**Type:** Codeine, dextropropoxyphene, ethylmorphine and dextromethorphan **Route:** Not reported **Length of use:** Not clearly reported (Dichotomised into regular and irregular use)	Dose was not taken into account.	N/A	N/A
Raja et al. (2002)	**Type:** Controlled-release morphine **Route:** Not reported **Length of use:** 8 weeks	91mg/d (15mg/d to 225 mg/d)	91mg (15mg to 225 mg)	91mg (15mg - 225 mg)
	Type: Methadone (Alternative to morphine) **Route:** Not reported **Length of use:** 8 weeks	15 mg/d	150mg	150mg

Figure 1 PRISMA Flowchart (48)

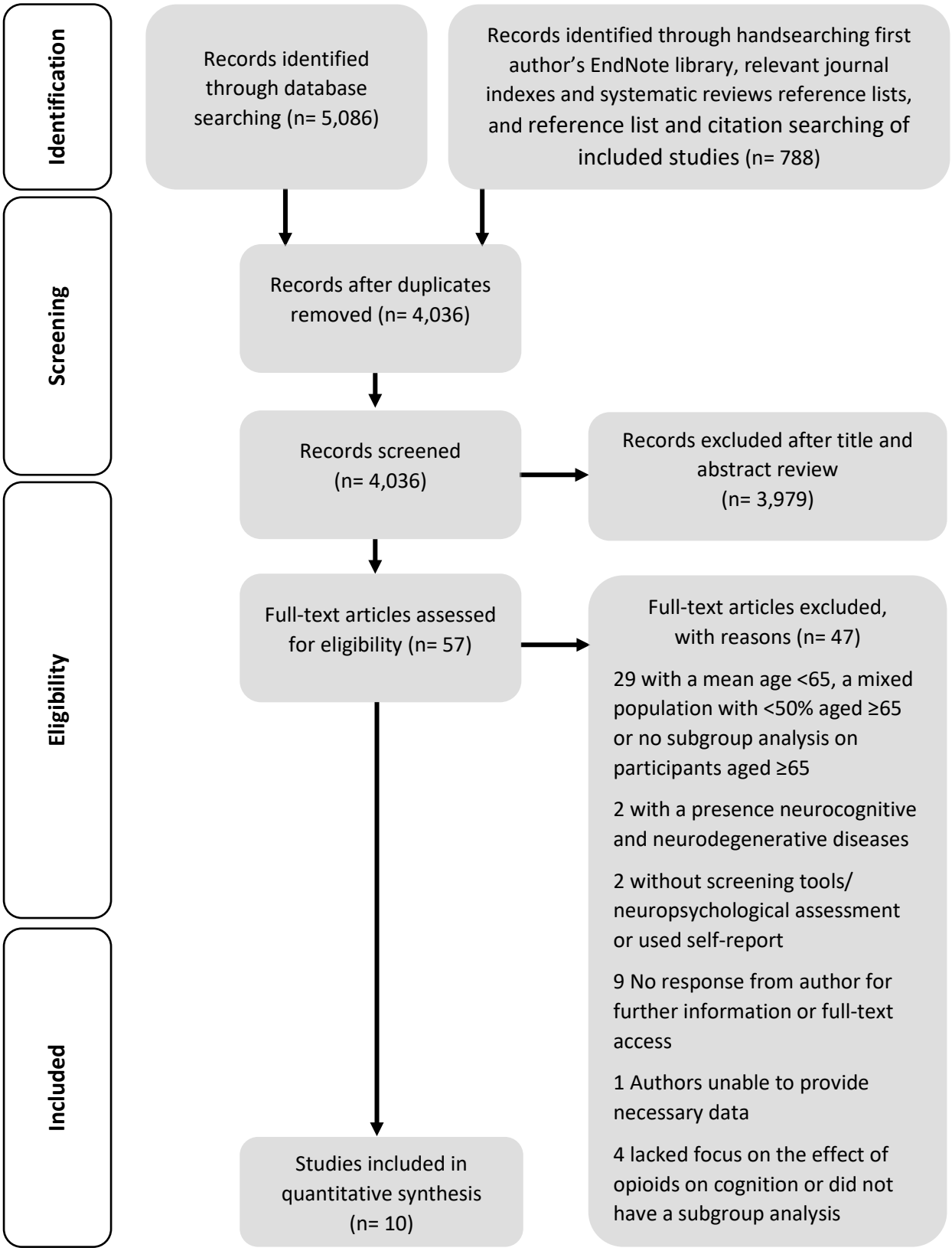
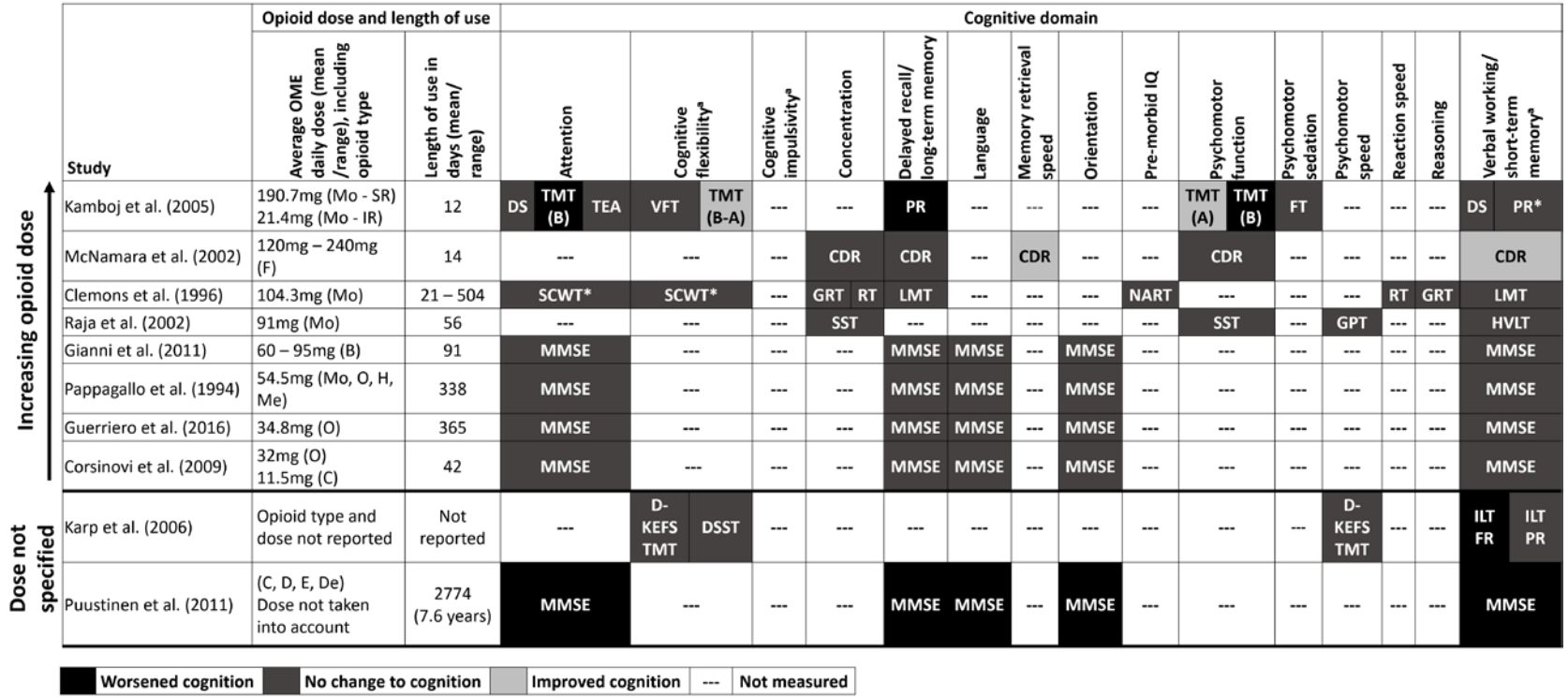


Figure 2. Impact of opioids on cognition, mapped by cognitive domain



Study	Average OME daily dose (mean /range), including opioid type	Length of use in days (mean/ range)	Attention	Cognitive flexibility[a]	Cognitive impulsivity[a]	Concentration	Delayed recall/ long-term memory	Language	Memory retrieval speed	Orientation	Pre-morbid IQ	Psychomotor function	Psychomotor sedation	Psychomotor speed	Reaction speed	Reasoning	Verbal working/ short-term memory[a]
Kamboj et al. (2005)	190.7mg (Mo - SR) 21.4mg (Mo - IR)	12	DS, TMT (B), TEA	VFT, TMT (B-A)	---	---	PR	---	---	---	---	TMT (A), TMT (B)	FT	---	---	---	DS, PR*
McNamara et al. (2002)	120mg – 240mg (F)	14	---	---	---	CDR	CDR	---	CDR	---	---	CDR	---	---	---	---	CDR
Clemons et al. (1996)	104.3mg (Mo)	21 – 504	SCWT*	SCWT*	---	GRT, RT	LMT	---	---	---	NART	---	---	---	RT	GRT	LMT
Raja et al. (2002)	91mg (Mo)	56	---	---	---	SST	---	---	---	---	---	SST	---	GPT	---	---	HVLT
Gianni et al. (2011)	60 – 95mg (B)	91	MMSE	---	---	---	MMSE	MMSE	---	MMSE	---	---	---	---	---	---	MMSE
Pappagallo et al. (1994)	54.5mg (Mo, O, H, Me)	338	MMSE	---	---	---	MMSE	MMSE	---	MMSE	---	---	---	---	---	---	MMSE
Guerriero et al. (2016)	34.8mg (O)	365	MMSE	---	---	---	MMSE	MMSE	---	MMSE	---	---	---	---	---	---	MMSE
Corsinovi et al. (2009)	32mg (O) 11.5mg (C)	42	MMSE	---	---	---	MMSE	MMSE	---	MMSE	---	---	---	---	---	---	MMSE
Karp et al. (2006)	Opioid type and dose not reported	Not reported	---	D-KEFS TMT, DSST	---	---	---	---	---	---	---	---	---	D-KEFS TMT	---	---	ILT FR, ILT PR
Puustinen et al. (2011)	(C, D, E, De) Dose not taken into account	2774 (7.6 years)	MMSE	---	---	---	MMSE	MMSE	---	MMSE	---	---	---	---	---	---	MMSE

Opioids; (B): Buprenorphine, (C): Codeine, (D): Dextropropoxyphene, (De): Dextromethorphan, (E): Ethylmorphine, (F): Fentanyl, (H): Hydromorphone, (O): Oxycodone; (Me): Methadone, (Mo): Morphine, IR: Immediate release, SR: Sustained release.

Screening tools and neuropsychological tests; CDR: Cognitive Drug Research computerised assessment, D-KEFS TMT: Delis-Kaplan Executive Trail Making Test, DS: Digit Span, DSST: Digit Symbol Subtest, FT: Finger Tapping, GPT: Grooved Pegboard Task, GRT: Grammatical Reading Test, HVLT: Hopkins Verbal Learning Test, ILT: Incidental Learning Test (including free recall and paired recall), LMT: Logical Memory Test, MMSE: Mini-mental State Examination, NART: National Adult Reading Test, PR: Prose Recall, RT: Reaction Time, SCWT: Stroop Colour-Word Test, SST: Symbol Substitution Task, TEA: Tests of Everyday Attention, TMT(A): Trail Making Test (Part A), TMT(B): Trail Making Test (Part B), TMT(B-A): Trail Making Test (Part B – Part A), VFT: Verbal Fluency Test.

[a] Cognitive domain from Baldacchino et al. 2012

* No significant change to cognition but authors acknowledged a trend towards a decline in performance