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[Intervention Review]

Opioids for agitation in dementia

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ABSTRACT

Background

Agitation is a common experience for people living with dementia, particularly as day-to-day function and cognition start to decline more. At the present time there are limited pharmacological options for relieving agitation and little is known about the safety and efficacy of opioid drugs in this setting.

Objectives

To determine the clinical efficacy and safety of opioids for agitation in people with dementia.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group Specialized Register, on 13 June 2014 using the terms: narcotic OR opioid OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol OR methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone.

ALOIS contains records of clinical trials identified from monthly searches of a number of major healthcare databases such as MEDLINE, EMBASE and PscyINFO, as well as numerous trial registries and grey literature sources.

Selection criteria

Randomised, controlled trials of opioids compared to placebo for agitation in people with dementia.

Data collection and analysis

Two authors independently assessed the studies identified by the search against the inclusion criteria.

Main results

There are currently no completed randomised, placebo controlled trials of opioids for agitation in dementia. There are two potentially relevant trials still in progress.

Authors' conclusions

We found insufficient evidence to establish the clinical efficacy and safety of opioids for agitation in people with dementia. There remains a lack of data to determine if or when opioids either relieve or exacerbate agitation. More evidence is needed to guide the effective, appropriate and safe use of opioids in dementia.

PLAIN LANGUAGE SUMMARY

Opioids for agitation in dementia

Opioids (such as morphine and codeine) are strong painkillers best known as treatments for post-surgical and cancer pain. They are also used for long-term painful conditions other than cancer and sometimes for symptoms other than pain. They have a number of important adverse effects and their use involves a balance of risks and benefits.

Agitation is a common experience for people living with dementia. Usual treatment initially focuses on identifying and remedying underlying causes and meeting unmet needs. If agitation persists, then drug treatments are often used. However, the current drug treatments for relieving agitation have limited effectiveness and are associated with safety concerns.

Pain may be one cause of agitation in dementia. Many people with dementia (particularly older people) will also have chronic, painful conditions. Pain may be experienced differently due to the dementia and may often go uncommunicated or untreated. It can be hard to know whether agitation is due to pain. Opioids may be useful in the treatment of agitation where pain is an underlying factor, but may also be effective for relieving distress in the absence of physical pain.

We searched for randomised, placebo controlled trials in which people with any form of dementia and associated agitation were treated with opioid drugs. We found no completed trials to include in our review, although there are two potentially relevant trials still in progress.

We therefore concluded that there is no high quality evidence to determine whether opioids are a safe or effective treatment for agitation in dementia.

BACKGROUND

Description of the condition

Dementia is a syndrome caused by an acquired decline in brain function, which is usually progressive. It is caused by a number of disorders of which Alzheimer's disease is the most common. It is estimated to affect approximately 5% of the world population aged 60 years or over (Alzheimer's Disease International 2009). Diagnostic assessment often focuses on cognitive features but the most significant symptoms causing patient distress and carer burden in later stages are the so called behavioural and psychological symptoms of dementia (BPSD). Three broad BPSD syndromes are recognised, psychosis, mood disorders and agitation (Finkel 1996). A frequently cited definition of agitation is "inappropriate verbal, vocal, or motor activity that is not explained by the needs or confusion of the agitated individual" (Cohen-Mansfield 1986). Factor analysis tends to identify four subgroups of agitated behaviours, aggressive behaviour (often associated with personal care, such as hitting, scratching, biting or verbal aggression); physically non-aggressive behaviour (such as pacing, trying to get to a different place, restlessness, inappropriate disrobing); verbally agitated behaviour (such as calling out); and hiding and hoarding (Rabinowitz 2005).

Agitation is present in approximately 20% of the people with Alzheimer's disease in contact with clinical services (Burns 1990; Lyketsos 2000) and up to 48% to 82% of those residing in care facilities (Zuidema 2007). Most guidelines for the assessment and management of agitation advocate a holistic approach, addressing physical health needs, screening for undetected pain, consideration of medication side effects, treating depression, and developing a care plan with carers that takes account of psychosocial, environmental and biographical factors as well as a behavioural and functional analyses of the specific symptoms. A variety of non-pharmacological treatment modalities exist but prescribing continues to have a role, especially where there is severe distress or immediate risk of harm to the person or others. Antipsychotic drugs have tended to be the mainstay of treatment although their over-prescription, effectiveness and harmful effects have been a source of concern (Banerjee 2009; Schneider 2005; Schneider 2006). Alternatives have a limited evidence base. Opioids represent a largely unexplored avenue despite their wide use in a broad range of conditions and care settings. Opioids have a clear role for the treatment of pain, which a number of observational studies indicate is under-recognised in dementia (Bernabei 1998; Morrison 2000), possibly because of decreased ability to communicate. While pain is an obvious target for opioids, experience in palliative care settings suggests that there may be a broader role for opioids in the relief of more general distress (Fainsinger 2000). To date, a small number of case reports, case series and other evaluations have begun looking at a specific role for opioids for agitation in dementia (Kurrle 1995; Manfredi 2003; Passmore 2011; Sloan 1989). Others have incorporated opioids as part of a systematic approach to detecting and treating pain in this setting (Husebo 2011 a).

Description of the intervention

Opioids exert their action at opioid receptors, which are widely distributed in tissues around the body. Large numbers of receptors are present in the dorsal horn of the spinal cord, where they exert well known, powerful effects on the modulation of pain, as well as in the brain and brainstem.

There are over 20 different opioid drugs available in a variety of formulations, including immediate and modified release tablets, oral solutions, transdermal patches and injectables. As well as their analgesic effects, they also have non-analgesic uses including the relief of breathlessness in advanced lung disease, for cough suppression and diarrhoea. Their usefulness in palliative care settings may be through multiple mechanisms and, in particular, they can relieve general fear and distress through sedative and anxiolytic effects as well as by conferring a sense of well-being. Observation of this important general role in relieving distress has been considered relevant to the search for treatments for agitation in dementia (Brown 2010; Kurrle 1995).

Opioids have a significant number of predictable side effects. These include nausea and vomiting (particularly in the early stages of treatment), constipation, dry mouth and sedation or somnolence. The latter is particularly relevant to studies addressing agitation. Larger doses may be associated with respiratory depression. There is also some evidence specific to older people, some of which has highlighted risks such as delirium, confusion, falls and fracture risk, all of which are relevant to a large proportion of people with dementia (McLachlan 2011; O'Neil 2012; Papaleontiou 2010). No studies appear to have been conducted to specifically evaluate the effect of opioids on pain in patients with dementia and therefore we know little about the risks of opioids in this vulnerable group of patients.

How the intervention might work

Opioids have a well established role for the relief of acute pain and post-surgical pain, and there is some evidence for their use in the management of chronic non-cancer pain (Cochrane 2010). Opioids do not currently have an established role as a targeted therapy in neurodegenerative disorders or for specific psychological or behavioural symptoms. Three broad theoretical approaches may be taken to assess their effectiveness in such conditions. These different approaches will be reflected in differences in the study question, trial design, how the link between pain and agitation is handled when addressing confounding factors (such as existing drugs and painful conditions) and such issues as the theoretical risk of masking painful conditions.

Firstly, opioid use may form part of a broader systematic approach to the detection and treatment of pain. While it can be difficult to detect pain in advanced dementia, a small number of studies have incorporated methods to improve detection of pain to address agitation, including at least one that explicitly included opioids in a treatment algorithm (Husebo 2011 a).

A second, more pragmatic approach can be taken. Reliably detecting pain can be difficult. Most pain detection tools identify non-specific agitation. Discriminating between agitation caused by pain and other causes is a significant methodological challenge. Given the high risk of undetected pain in those unable to report it, simply adding low dose opioids to all who are significantly agitated might reduce agitation by treating undetected pain (Manfredi 2003).

A third approach is to use opioids to target more general 'distress' and 'psychological pain' underlying agitation, as well as somatic

pain. This links with clinical observations of the practical use of opioids in relieving 'distress' in other palliative and chronic disease settings. A precise mechanism by which opioids might do this has not been elucidated. Endogenous opioid systems are known to play a part in a variety of higher-order neurobiological functions including affect, fear, stress, reward, aggression, memory, appetite and response to emotionally salient stimuli (Bodnar 2010; Leknes 2008; Zubieta 2001; Zubieta 2003). The neural basis for these functions is poorly understood and is largely derived from animal studies and a small number of studies using in vivo neuroimaging paradigms in humans.

Why it is important to do this review

Relieving agitation in people with dementia requires a person-centred approach that makes sense of the underlying causes and unmet needs and addresses these directly. This may well include the detection and treatment of pain. There will often be a range of interventions for agitation but, where prescribing is considered, atypical antipsychotics have historically been the mainstay of drug treatment despite only very modest efficacy. The evidence to date supports only short-term use, particularly in aggression (Cochrane 2006; Sultzer 2008); and highlights serious side effects, including stroke and death (Schneider 2005; Schneider 2006), as well as decreased quality of life and accelerated cognitive decline (Ballard 2009). Accordingly, in the UK, the Chief Medical Officer and a more recent UK government funded report (Banerjee 2009) have recommended judicious use of these drugs, as has the Food and Drug Administration (FDA) in the US. There is, therefore, an urgent need to explore the potential benefits and risks offered by alternative classes of drugs, including opioids. The most promising alternatives to antipsychotics are some antidepressants (Cochrane 2011; Porsteinsson 2014) and possibly carbamazepine (Tariot 1998), which still needs investigation with larger placebo controlled trials to demonstrate clear efficacy. Memantine does not seem to improve clinically significant agitation in people with in moderate-to-severe Alzheimer's disease (Fox 2012). There is now a growing body of evidence looking at the role of analgesics and opioids in treating agitation and it is timely to complete a formal systematic review.

OBJECTIVES

To determine the clinical efficacy and safety of opioids for agitation in people with dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) (including cluster RCTs and cross-over trials). Given the lack of RCTs, other types of study have been discussed in the 'Background' and 'Discussion' sections of the review, but have not been taken into account as evidence of efficacy.

Types of participants

Any age and either sex.

Setting: all settings including hospital and care homes.

Diagnosed with dementia of any type and severity, or cognitive impairment according to internationally accepted criteria such as National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann 1984), Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) or International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10).

Other measurements to assess cognitive function, such as Mini-Mental State Examination (MMSE) (Folstein 1975), Clinical Dementia Rating (CDR) (Hughes 1982), Global Deterioration Scale (Reisberg 1982); and other medical, psychiatric or psychological evaluations were accepted in the absence of these measures.

Participants were required to be selected for the presence of agitation at baseline using an appropriate, validated tool such as the Cohen-Mansfield Agitation Inventory (Cohen-Mansfield 1989) or the Neuropsychiatric Inventory (NPI) (Cummings 1994).

Types of interventions

Any opioid given at any dose and for any time period compared with placebo. The term opioid was taken to include both synthetic and opiate narcotics. The term opioid was taken to encompass only agonists (for example morphine) and partial agonists (for example buprenorphine) and excluded antagonists (for example naloxone).

Types of outcome measures

Primary outcomes

The primary outcome was reduction in agitation at the end of the scheduled follow-up. We specified that the endpoint should be assessed by recognised measures of agitation, such as the Cohen-Mansfield Agitation Inventory (Cohen-Mansfield 1989) or the NPI (Cummings 1994), and defined by change from baseline or final value scores, or the patient no longer meeting the criteria for significant agitation (however defined).

We considered measures of safety and acceptability of treatment including the incidence of adverse effects (to include mortality, nausea and vomiting, constipation, dry mouth, sedation, confusion, mood changes, hallucinations etc.) and dropout rates, and reasons for withdrawal.

Primary outcomes are to be included in a 'summary of findings' table.

Secondary outcomes

Validated measures of quality of life such as DEMQOL (Smith 2005) and measures of carer burden.

For comparison with other interventions, such as antipsychotics, we were interested in measures of cognitive decline and the effects on other behavioural and psychological symptoms (BPSD).

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group Specialized Register, on 13 June 2014. Previous searches were run on 10 June 2012 and 22 June 2013. The search terms used were: narcotic

OR opioid OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol OR methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone.

ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) and it contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from the following.

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS.
2. Monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organization (WHO) International Clinical Trials Registry Portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials; the Netherlands National Trials Register, plus others).
3. Quarterly searches of the Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources that are searched for ALOIS see About ALOIS on the website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

Searching other resources

Other search strategies

1. Conversations with clinical colleagues (particularly those who have co-ordinated trials in dementia)
2. Contacting key authors who have published in this field
3. Conference proceedings where available
4. Internet searches
5. Forward and backward citation searches of included studies
6. Handsearching of key journals (including International Psychogeriatrics; Journal of Pain and Symptom Management, Age and Ageing; the International Journal of Geriatric Psychiatry; Journal of the American Geriatric Society; and The American Journal of Geriatric Psychiatry) for years not already covered by ALOIS.

Data collection and analysis

Selection of studies

Two review authors screened abstracts of all identified studies against the inclusion criteria (ES, RB). We retrieved all possibly relevant articles in full text for comprehensive assessment against the inclusion criteria. An effort was made to obtain translations of non-English language papers sufficient to judge their suitability for inclusion. There were no differences in study selection between review authors.

Data extraction and management

We customised the CDCIG data extraction form for the review. Where possible, the following information was obtained for each study.

- The number of patients eligible, number randomised, and reasons why patients were not included in the trial.
- The number of patients evaluated at follow-up(s) and what the follow-up time points were.
- Patient characteristics including age, sex, co-morbidities, diagnosis and type of dementia, type of healthcare or community setting, stage or severity of disease (for example, as measured by MMSE or CDR).
- Trial design features on masking, whether parallel group or cross-over, features of randomisation, and sample size calculation.
- Any necessary additional data on trial design and outcomes to allow completion of the Cochrane Collaboration's tool for assessing risk of bias.
- Comparison intervention including duration and mode.
- Outcome data at all time points, including how outcome was measured and the mean or categorical scores of the main and other outcomes.
- Measures of sedation and efforts to correct for this statistically.
- Measures of pain and efforts to correct for this statistically.
- Comment on success of masking, given the possibility of side effects unmasking patients.
- Adverse effects, dropout rates and reasons why.
- Concurrent use of other drugs including analgesics, and exclusions.
- Measures of cognition or cognitive decline during or after the intervention, or both.
- Quality of life and carer burden, and how these were measured.
- Other behavioural and psychiatric symptoms of dementia and the scales used to measure them.

Two review authors (RB and ES) extracted data independently. Where information was lacking, we attempted to make contact with trial authors or trial sponsors.

Assessment of risk of bias in included studies

We have assessed and reported on the risk of bias of included RCTs using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2009). This recommends the explicit reporting of the following quality elements for RCTs: sequence generation; allocation concealment; blinding; completeness of outcome data; and selective outcome reporting. For each quality domain we assessed whether there was a low risk of bias (if the study matched

the criteria), a high risk (if the study did not match the criteria) or unclear risk of bias (because of under-reporting). We defined trials as having an overall low risk of bias if they scored a low risk of bias on four of the five domains in the risk of bias table. We have labelled a trial as having an unclear risk of bias if the trial provided too few details to make a judgement of 'high' or 'low' risk of bias.

We assessed the risk of bias of included studies, with disagreements resolved by discussion and consensus. Where indicated, we contacted study authors for additional information. We incorporated the results of the risk of bias assessment into the review through systematic narrative description and commentary about each item, leading to an overall assessment of the risk of bias of included studies and a judgement about the internal validity of the review's results.

Measures of treatment effect

The null hypothesis to be tested was that, for the primary outcomes examined, opioids have no effect compared with placebo or a comparator.

Studies measuring treatment effect can present either continuous data or dichotomous data.

Where present, we used numeric scores such as those provided by the Cohen-Mansfield Agitation Inventory (Cohen-Mansfield 1989) to measure response to treatment. We planned to review scalar assessments of agitation, for example the Multidimensional Observation Scale for Elderly Subjects (MOSES) (Helmes 1987), where available. It was planned that effect measures for ordinal data reported in a RCT would be assessed as continuous data where appropriate.

For continuous variables, or ordinal variables approximated to continuous variables, the summary statistics required for each trial were either the change from baseline scores or final endpoint scores at follow-up. The choice of effect measure would be determined by whether or not outcomes in different studies were assessed using the same scale. If this was the case, it was planned that the mean difference (MD) would be used. Where not, the standardised mean difference (SMD) would be calculated.

Because of a potentially wide variation in the way the response to treatment is measured, we anticipated that it may be necessary in some instances to operationalise outcomes dichotomously as simply 'improved' versus 'not improved', regardless of the scale used by the authors. This would be more appropriate where there is a defensible cut-off score established in the literature. We planned to generate risk ratios (RRs) and their 95% confidence intervals (CIs) where dichotomous data were reported in a RCT.

Unit of analysis issues

We planned to use the intra-cluster correlation coefficient (ICC) to estimate the effective sample size In the event that we identified a trial using a cluster design (in which participants were randomised at group level). If cross-over trials had been included in a meta-analysis, we would have sought specialist advice from the CDCIG.

Dealing with missing data

The primary aim of the review was to obtain standardised data through collaboration with the original investigators. Where data were missing from published reports we contacted the primary investigator to try and get the information. Where we were unable to obtain data, we have stated that.

Missing studies can result from an inadequate search for data or from publication bias in that papers with negative findings are less likely to be published. Our approach to this is detailed in the section on our search strategy and the section on reporting bias.

Loss to follow-up may present an issue and we have reported attrition rates, per trial, in the 'risk of bias' tables.

We planned to undertake a 'sensitivity to missing data' analysis where dichotomous data were missing and it had been possible to do an analysis. We will address the potential impact of missing data on our findings in the 'Discussion' section of the review.

Assessment of heterogeneity

If a meta-analysis had been possible, we would have used the Chi^2 test and I^2 statistic to evaluate heterogeneity between trials (Higgins 2009). We would have considered a Chi^2 test P value of less than 0.10 or an I^2 value equal to or more than 50% as indicative of substantial heterogeneity.

Assessment of reporting biases

We planned to assess publication bias by using funnel plots had we identified a sufficient number of studies to make a meta-analysis possible.

Data synthesis

If they were available, sufficiently similar and of sufficient quality, we planned to combine the data statistically across trials. We would have used a fixed-effect (FE) model (Mantel-Haenszel method) in the first instance. We would have used a random-effects (RE) model (DerSimonian and Laird) to check the robustness of the FE model if there was no substantial heterogeneity. We would have used the RE model a priori if substantial statistical heterogeneity was observed.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses if heterogeneity was identified between trials included in a meta-analysis.

1. Age of patient (years) by deciles: 60 to 69; 70 to 79; 80 to 89; 90 and older.
2. Type of dementia, whether Alzheimer's disease, vascular dementia, Lewy body or a rarer syndrome.
3. Severity of dementia as determined by the MMSE score (e.g., mild: 19 to 16; moderate: 15 to 10; severe: 9 to untestable), or other appropriate measures such as the CDR.
4. Baseline severity of agitation.
5. Baseline severity of pain.

Sensitivity analysis

Had there been sufficient trials we planned to perform sensitivity analyses in order to explore the influence of the following factors, by:

1. excluding unpublished studies (if there were any);
2. taking account of study quality (low or high risk of bias, as defined above);

3. sensitivity to missing data analysis for dichotomous data, where required.

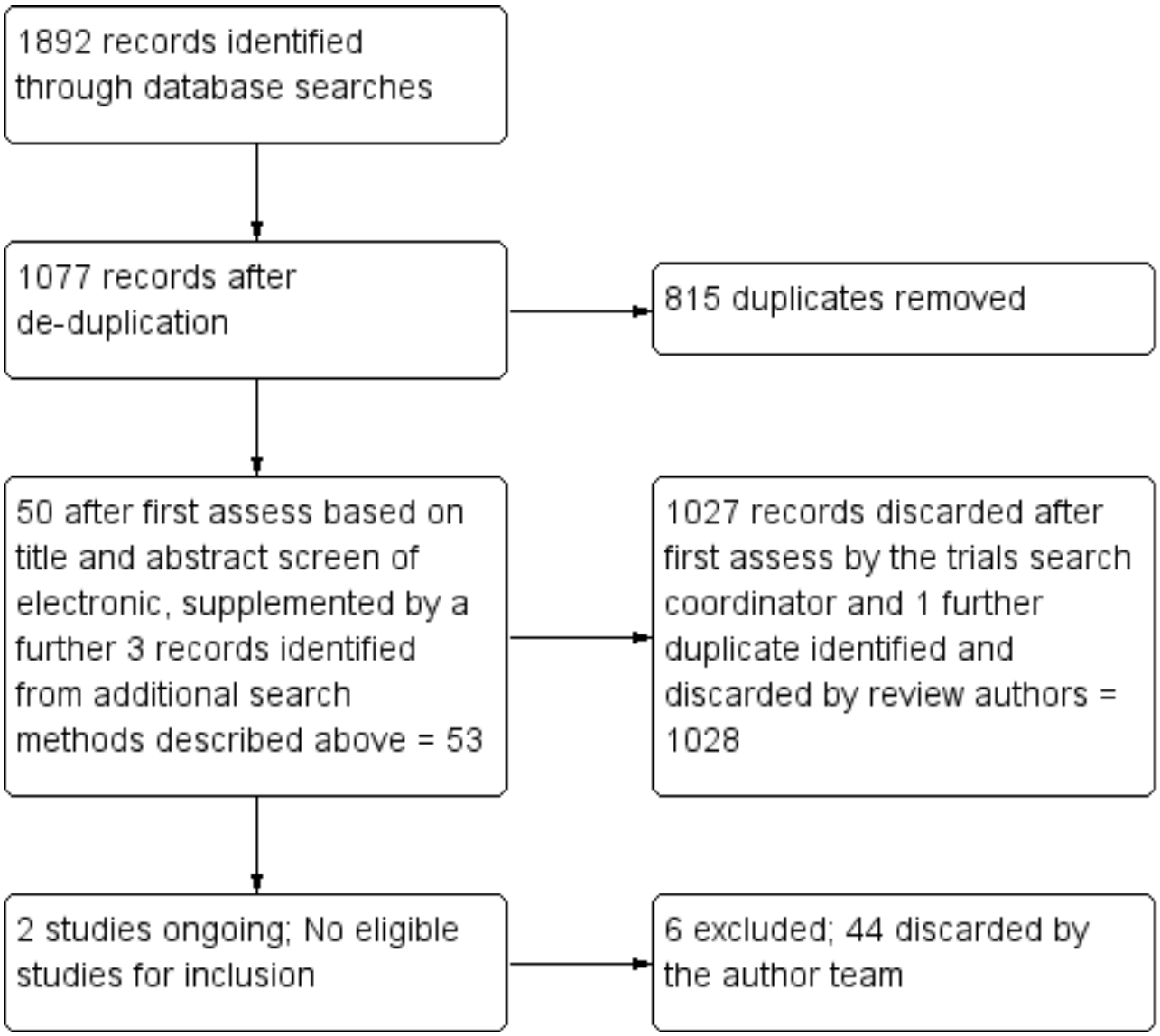
RESULTS

Description of studies

Results of the search

The electronic search (most recently performed in June 2014) retrieved a total of 1892 results. After a first assessment and de-duplication of these results the authors were left with 50 references to further assess. These included two studies registered as being in process (Gibson 2011; L-DOT study). One further small case series was found through Internet searching (Kurrle 1995) and one further case report by handsearching (Passmore 2011). The electronic search identified one RCT that did not include a placebo comparison (Husebo 2011). Handsearching identified a further published paper about aspects of the same trial (Husebo 2014). We found no completed randomised, placebo controlled trials. See Figure 1.

Figure 1. Study flow diagram.



Included studies

No studies met our inclusion criteria. Two identified studies are ongoing and we have contacted both chief investigators (Gibson 2011; L-DOT study), see Characteristics of ongoing studies.

Excluded studies

Two authors (ES and RB) reviewed the total 50 references identified after initial de-duplication and the first assessment of titles and abstracts by the Trials Search Co-ordinator. A further three papers were identified by the additional search strategies. One was discarded as a duplicate; 17 were discarded because they did not relate to people with dementia (nearly all were papers relating to post-operative delirium); 24 were discarded because they did not

specifically address a question relating to agitation in dementia. Two papers on the subject of opioids for agitation in dementia were discarded because they were not clinical studies.

Of the remainder, one study was excluded because it did not study opioids (Buffum 2004). We identified one RCT that used opioids for agitation in dementia as part of a trial design but did not meet our criteria because it did not include a placebo component (Husebo 2011; Husebo 2014). Husebo et al's trial was a cluster RCT involving 352 participants in 60 clusters in 18 nursing homes in five municipalities of western Norway. Participants in the intervention group received individual daily treatment of pain for eight weeks, according to a step-wise protocol, with paracetamol (acetaminophen), morphine, buprenorphine transdermal patch or pregabalin. The control group received usual treatment and care. Four remaining studies identified by the search strategy and obtained in full were excluded because they were not RCTs. These included two case reports (Passmore 2011; Sloan 1989), one case series (Kurrle 1995) and a non-randomised trial with a novel design (Manfredi 2003), see also Characteristics of excluded studies and the Discussion.

Risk of bias in included studies

There were no included studies.

Effects of interventions

There were no eligible trials to provide data and allow comment on the effects of interventions.

DISCUSSION

Summary of main results

Our review identified no eligible trials, with two potentially relevant trials still in progress. One excluded trial (Husebo 2011 a) did however show that a systematic approach to assessing and treating pain, which included the use of opioids in some participants, significantly reduced agitation in residents of nursing homes with moderate to severe dementia. However, not all subjects in this trial received opioids as part of the intervention and the trial did not include use of a placebo.

Overall completeness and applicability of evidence

We found insufficient evidence to establish the clinical efficacy and safety of opioids for agitation in people with dementia. This is because there were no randomised trials that were placebo controlled.

In one excluded study, the intervention coupled with a systematic approach to the assessment of pain appeared to reduce agitation but it should be noted that only 22% of participants received an opioid, the intervention of interest (Husebo 2011). This was nonetheless an important pragmatic clinical study that reflects a standard clinical approach to pain management using an analgesic ladder (modelled on the first American Geriatric Society guideline (AGS Clinical Practice Guideline 1998) and echoing the WHO analgesic ladder for cancer pain). The AGS guideline has since been revised (AGS Clinical Practice Guideline 2009). The authors used a systematic approach to assessing pain by using the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) pain scale (Husebo 2010). This consists of a variety of elements including guided movements to assess musculoskeletal pain, explicit guidance to attend to a variety of pain behaviours, a survey of other body areas and a Likert pain scale for each domain. This echoes many, but does not necessarily address all, of the basic principles of assessment outlined by the AGS panel, which include observing for non-verbal behaviours, a timely and thorough physical examination, ensuring basic comfort needs are being met (for example hunger, thirst, toileting, loneliness, fear) and ruling out other causative pathologies (for example urinary retention, constipation, infection). Notably, the AGS guideline advocates an empirical trial of analgesia, which remains a contentious intervention especially where opioids are considered.

While Husebo provided information on side effects and tolerability, mentioning that nine participants on the step-wise protocol were withdrawn due to a range of side effects, including drowsiness, nausea, acute psychiatric illness and skin allergic reaction, in contrast to none on the treatment as usual arm, they do not specify which analgesic drug treatment these participants were on. Of these nine, three participants had drowsiness and nausea. It is recognised that agitation may appear to have declined predominantly as a result of the sedative effects of opioid analgesics. The authors suggested that as few participants (n = 3) were excluded because of drowsiness and nausea (it is not clear whether these three were on opioids), and as neither activities of daily living nor cognition worsened in the treatment group compared with control group (although the subgroup on opioids was not specifically looked at), sedation could not explain the reduction of agitation in the active group. The study did not include a specific measure of sedation to allow for statistical correction.

Husebo assessed fairly severely impaired people with dementia. This only provided evidence for severe dementia (median MMSE score 8, Functional Assessment Staging Test (FAST) score 6) and we do not know the impact on patients with more moderate dementia who might be seen in a clinic or be assessed in their own homes.

A study by Manfredi was excluded because it was not a RCT (Manfredi 2003), see also Quality of the evidence. With regard to tolerability, they found that adverse events such as nausea, falls and constipation were not statistically different in the two treatment phases, where the active treatment arm included either oxycodone 10 mg twice a day or long-acting oral morphine 20 mg once a day. To avoid constipation their participants were given combined docusate sodium and senna during the treatment phase with a matching placebo for the placebo phase.

Quality of the evidence

There was insufficient evidence to answer our question. Aspects of trial design in this area are worthy of discussion, however.

Any type of study in this area is methodologically challenging to conduct. One study used a cluster RCT but did not include a true placebo group; this may be difficult as it may not be an option to offer participants an ineffective placebo when other 'usual care' options are available (Husebo 2011). The design of the trial made blinding difficult. The authors described procedures to try and achieve the highest level of concealment possible but it may be that awareness of the trial design and management procedures was shared between individual care homes and care staff. Participants were allowed to continue on anti-dementia drugs and psychotropics if they remained stable on these for the four weeks prior to inclusion. Other human and health service

related factors that influence the care received in the homes are hard to quantify and may not have been fully controlled for by randomisation. Examples include knowledge and education around non-pharmacological approaches, and the quality of generic services going in to the homes in the intervention group (for example anaesthetic or palliative care in-reach for care homes); these might have been explicitly identified and stratified for.

A major methodological challenge with any type of study in this area is to establish whether agitation is primarily due to pain and whether there are other sources of distress. There are no well validated assessments of agitation in dementia with properties to allow this distinction. However, given the clinical difficulty of making this distinction, more pragmatic trials may not necessarily wish to try and do so.

The Manfredi study (Manfredi 2003) was excluded from our review as it was not truly randomised, having an unconventional but interesting methodology using a 'faux cross-over' or 'concealed before and after' design. This would be hard to replicate due to problems with blinding. In contrast to the Husebo trial, it did measure and control for sedation and tried to control for pain by excluding those who were able to complain of pain and who had an obviously painful condition.

Potential biases in the review process

Two trials were identified with data not yet available (Gibson 2011; L-DOT study).

Our primary question may not be framed pragmatically. Choosing just opioid analgesics has arguably limited the trials for inclusion, with paracetamol (acetaminophen) trials excluded. This does not marry well with current routine practice, which takes a step-wise approach to prescribing beginning with simple analgesia such as that provided by paracetamol and then increasing the treatment as necessary to stronger analgesics such as opioids. There is scope in the future to revise the review to consider a broader question of analgesia for agitation.

Agreements and disagreements with other studies or reviews

Husebo completed a systematic review of English and German language papers regarding pain treatments for agitation in dementia using the PubMed and Cocharane databases, between 1992 and 2010 (Husebo 2011 b). This review identified studies that included paracetamol (acetaminophen) as well as the Manfredi trial. They reached a similar conclusion about the lack of robustly designed and powered clinical trials. Pieper et al have also published a review (Pieper 2013) identifying similar studies with similar conclusions about their limitations.

AUTHORS' CONCLUSIONS

Implications for practice

There was insufficient evidence to determine whether or not opioids are effective and safe for treating agitation in dementia, whether they are tolerated by people with dementia, or indeed whether they may increase agitation.

Implications for research

Randomised placebo controlled trials of opioids for agitation in dementia are needed.

Such studies should investigate the tolerability and safety of opioids. This would be best achieved using a placebo design. Agitation is a complex phenomenon and it would be useful for trials to seek to identify those manifestations of agitation that best respond to the intervention and what level of agitation warrants treatment. A more challenging task would be to identify those causes of agitation that best respond to the intervention, including how to more reliably distinguish agitation caused by pain.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Buffum 2004	A double blind, placebo controlled cross-over trial, excluded as it examined acetaminophen (paracetamol) and not opioids
Husebo 2011	A cluster randomised controlled trial involving 352 participants, in 60 clusters in 18 nursing homes in five municipalities of western Norway. Participants in the intervention group received individual daily treatment of pain for eight weeks according to a step-wise protocol, with paracetamol (acetaminophen), morphine, buprenorphine transdermal patch, or pregabalin. The control group received usual treatment and care. Excluded because not all participants received an opioid and there was no placebo arm
Kurrle 1995	Case series of 16 patients with severe dementia in a care home setting and treated with oral morphine, including six where morphine was given specifically for agitation, restlessness or disruptive behaviour such as calling out or shouting. Excluded because it was not a randomised controlled trial
Manfredi 2003	Study uses a novel trial design, a concealed 'before and after' design. Placebo was administered for 4 weeks and then a long-acting opioid for 4 weeks. Patients and study nurses did not know whether placebo or opioid was administered. Although placebo was used, the trial was excluded as it was not a truly randomised trial
Passmore 2011	Case report of a single patient with dementia, incident pain with agitation treated with the short-acting opioid sufentanil administered sublingually before personal care. Excluded because it was not a randomised controlled trial
Sloan 1989	Case report of two patients with severe dementia due to Huntington's disease treated with oral morphine. Excluded because it was not a randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Gibson 2011

Trial name or title	Pain relief as a treatment for agitation and aggression in persons with dementia
Methods	Randomised controlled trial - parallel group assignment
Participants	Inclusion criteria: suffering from dementia, has pain (Abbey > 3), has BPSD (Cohen-Mansfield Agitation Inventory (CMAI) > 12), normal liver and kidney function Exclusion criteria: taking current analgesics, clinically unstable
Interventions	Arm 1: paracetamol (acetaminophen) (1000 mg four times daily for two weeks; given orally as part of a pink pain mixture) Arm 2: codeine (30 mg four times daily for two weeks; given orally as part of a pink pain mixture) Comparator: placebo (pink pain mixture four times daily for two weeks; mixture contains flavoured syrup; given orally)
Outcomes	Primary outcome: CMAI and pain scores (Abbey pain scale, Pain Assessment in Advanced Dementia (PAINAD), Pain Assessment Checklsit for Seniors with Limited Ability to Communicate (PACSLAC)) after two weeks of analgesic treatment
Starting date	Anticipated date of first participant enrolment: 1/03/2011
Contact information	Prof Stephen Gibson, PhD s.gibson@nari.unimelb.edu.au

Gibson 2011 *(Continued)*

Notes	Still recruiting: no data available

L-DOT study

Trial name or title	Low-Dose Opiate Therapy for Discomfort in Dementia (L-DOT)
Methods	Double blind, double dummy, placebo controlled cross-over RCT
Participants	Patients over age 55 y with dementia residing in a nursing home care unit (or at home who receive care) at Tuscaloosa VAMC who demonstrate significant discomfort (as measured by PAINAD). Participants will be at an advanced stage of dementia demonstrated by a score of 6 or greater on the Functional Assessment Staging (FAST) scale and are unable to report pain in a reliable and consistent manner
Interventions	Arm 1. During the one-week experimental phase, the participants will receive hydrocodone/acetaminophen 2.5/167 mg per 5 ml liquid three times daily (TID), with liquid placebo available as needed (PRN) Arm 2. During the one-week experimental phase, the participants will receive a liquid placebo TID with hydrocodone/acetaminophen 2.5/167 mg per 5 ml liquid available PRN Arm 3. During the 6-week open-label phase, those who tolerate hydrocodone/acetaminophen 2.5/167 mg per 5 ml liquid three times daily (TID) during the double blind phase of the trial will enter a six-week, open-label extension phase of the study, receiving either hydrocodone/acetaminophen at the same dose or the most appropriate formulary alternative (for those who are judged to be responders during the double blind phase) or a higher dose (hydrocodone/acetaminophen 5/500 mg TID or the most appropriate formulary alternative). Participant can also receive up to 2 PRN at the same dose as listed above, but not to exceed 2.5 g of acetaminophen
Outcomes	Discomfort Battery (DB), Discomfort Scale for patient with Dementia Alzheimer's Type (DS-DAT) after 8 weeks
Starting date	October 2007
Contact information	A Lynn Snow, PhD MS BS, VA Medical Center, Tuscaloosa
Notes	Active, not recruiting

APPENDICES

Appendix 1. Sources searched and search strategies: June 2014

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	narcotic OR opioid OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol OR methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR	June 2012:13 June 2013: 2 June 2014: 0

(Continued)

	phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone	
2. MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1950 to present (OvidSP)	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/ 5. dement*.mp. 6. alzheimer*.mp. 7. (lewy* adj2 bod*).mp. 8. deliri*.mp. 9. (chronic adj2 cerebrovascular).mp. 10. ("organic brain disease" or "organic brain syndrome").mp. 11. ("normal pressure hydrocephalus" and "shunt*").mp. 12. "benign senescent forgetfulness".mp. 13. (cerebr* adj2 deteriorat*).mp. 14. (cerebral* adj2 insufficient*).mp. 15. (pick* adj2 disease).mp. 16. (creutzfeldt or jcd or cjd).mp. 17. huntington*.mp. 18. binswanger*.mp. 19. korsako*.mp. 20. or/1-19 21. Narcotics/ 22. *Analgesics, Opioid/ 23. narcotic*.ti,ab. 24. opioid*.ti,ab. 25. morphine.ti,ab. 26. Morphine/ 27. buprenorphine.ti,ab. 28. Buprenorphine/ 29. codeine.ti,ab. 30. Codeine/ 31. Dextromoramide/ 32. dextromoramide.ti,ab.	June 2012: 312 June 2013: 51 June 2014: 43

(Continued)

33. diphenoxylate.ti,ab.
34. Diphenoxylate/
35. dipipanone.ti,ab.
36. dextropropoxyphene.ti,ab.
37. Dextropropoxyphene/
38. propoxyphene.ti,ab.
39. diamorphine.ti,ab.
40. dihydrocodeine.ti,ab.
41. alfentanil.ti,ab.
42. Alfentanil/
43. fentanyl.ti,ab.
44. Fentanyl/
45. remifentanil.ti,ab.
46. meptazinol.ti,ab.
47. methadone.ti,ab.
48. Methadone/
49. nalbuphine.ti,ab.
50. Nalbuphine/
51. oxycodone.ti,ab.
52. Oxycodone/
53. papaveretum.ti,ab.
54. Opium/
55. pentazocine.ti,ab.
56. Pentazocine/
57. meperidine.ti,ab.
58. Meperidine/
59. pethidine.ti,ab.
60. phenazocine.ti,ab.
61. Phenazocine/
62. Hydrocodone/
63. hydrocodone.ti,ab.
64. hydromorphone/
65. hydromorphone.ti,ab.
66. Levorphanol/

(Continued)

67. levorphanol.ti,ab.
68. oxymorphone.ti,ab.
69. Oxymorphone/
70. butorphanol.ti,ab.
71. butorphanol/
72. dezocine.ti,ab.
73. sufentanil.ti,ab.
74. Sufentanil/
75. ketobemidone.ti,ab.
76. or/21-75
77. 20 and 76
78. randomized controlled trial.pt.
79. controlled clinical trial.pt.
80. randomi?ed.ab.
81. placebo.ab.
82. drug therapy.fs.
83. randomly.ab.
84. trial.ab.
85. groups.ab.
86. or/78-85
87. (animals not (humans and animals)).sh.
88. 86 not 87
89. 77 and 88

3. EMBASE 1980 to 2012 June 11 (OvidSP)	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/ 6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp.	June 2012: 309 June 2013: 151 June 2014: 72

(Continued)

10. (chronic adj2 cerebrovascular).mp.
11. ("organic brain disease" or "organic brain syndrome").mp.
12. "supranuclear palsy".mp.
13. ("normal pressure hydrocephalus" and "shunt*").mp.
14. "benign senescent forgetfulness".mp.
15. (cerebr* adj2 deteriorat*).mp.
16. (cerebral* adj2 insufficient*).mp.
17. (pick* adj2 disease).mp.
18. (creutzfeldt or jcd or cjd).mp.
19. huntington*.mp.
20. binswanger*.mp.
21. korsako*.mp.
22. CADASIL.mp.
23. or/1-22
24. narcotic agent/
25. narcotic analgesic agent/
26. narcotic*.ti,ab.
27. opioid*.ti,ab.
28. morphine.ti,ab.
29. morphine/
30. buprenorphine.ti,ab.
31. buprenorphine/
32. codeine.ti,ab.
33. codeine/
34. dextromoramide/
35. dextromoramide.ti,ab.
36. diphenoxylate.ti,ab.
37. diphenoxylate/
38. dipipanone.ti,ab.
39. dipipanone/
40. dextropropoxyphene.ti,ab.
41. dextropropoxyphene/
42. propoxyphene.ti,ab.
43. diamorphine.ti,ab.

(Continued)

44. dihydrocodeine.ti,ab.
45. alfentanil.ti,ab.
46. alfentanil/
47. fentanyl.ti,ab.
48. fentanyl/
49. remifentanil.ti,ab.
50. remifentanil/
51. meptazinol.ti,ab.
52. meptazinol/
53. methadone.ti,ab.
54. Methadone/
55. nalbuphine.ti,ab.
56. Nalbuphine/
57. oxycodone.ti,ab.
58. Oxycodone/
59. papaveretum.ti,ab.
60. Opium/
61. pentazocine.ti,ab.
62. Pentazocine/
63. hydrocodone.ti,ab.
64. Hydrocodone/
65. hydromorphone.ti,ab.
66. Hydromorphone/
67. Levorphanol/
68. Levorphanol.ti,ab.
69. oxymorphone.ti,ab.
70. Oxymorphone/
71. butorphanol.ti,ab.
72. Butorphanol/
73. dezocine.ti,ab.
74. sufentanil.ti,ab.
75. Sufentanil/
76. ketobemidone.ti,ab.
77. or/24-76

(Continued)

	78. 23 and 77	
	79. Randomized Controlled Trial/	
	80. Controlled Clinical Trial/	
	81. randomi?ed.ab.	
	82. placebo.ab.	
	83. drug therapy.fs.	
	84. randomly.ab.	
	85. trial.ab.	
	86. groups.ab.	
	87. ("double-blind*" or "single-blind*").ti,ab.	
	88. or/79-87	
	89. 78 and 88	
4. PsycINFO 1806 to June week 1 2012 (Ovid SP)	1. exp Dementia/ 2. exp Delirium/ 3. exp Huntingtons Disease/ 4. exp Kluver Bucy Syndrome/ 5. exp Wernickes Syndrome/ 6. exp Cognitive Impairment/ 7. dement*.mp. 8. alzheimer*.mp. 9. (lewy* adj2 bod*).mp. 10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp. 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp. 16. (cerebr* adj2 deteriorat*).mp. 17. (cerebral* adj2 insufficient*).mp. 18. (pick* adj2 disease).mp. 19. (creutzfeldt or jcd or cjd).mp. 20. huntington*.mp.	June 2012: 68 June 2013: 6 June 2014: 12

(Continued)

21. binswanger*.mp.
22. korsako*.mp.
23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp.
24. or/1-23
25. Narcotic Drugs/
26. exp Opiates/
27. narcotic*.ti,ab.
28. opioid*.ti,ab.
29. morphine.ti,ab.
30. exp Morphine/
31. buprenorphine.ti,ab.
32. codeine.ti,ab.
33. Codeine/
34. dextromoramide.ti,ab.
35. dipipanone.ti,ab.
36. dextropropoxyphene.ti,ab.
37. propoxyphene.ti,ab.
38. diamorphine.ti,ab.
39. dihydrocodeine.ti,ab.
40. alfentanil.ti,ab.
41. fentanyl.ti,ab.
42. remifentanil.ti,ab.
43. meptazinol.ti,ab.
44. methadone.ti,ab.
45. Methadone/
46. nalbuphine.ti,ab.
47. oxycodone.ti,ab.
48. papaveretum.ti,ab.
49. pentazocine.ti,ab.
50. meperidine.ti,ab.
51. pethidine.ti,ab.
52. phenazocine.ti,ab.
53. Hydrocodone.ti,ab.
54. hydromorphone.ti,ab.

(Continued)

	55. levorphanol.ti,ab. 56. oxymorphone.ti,ab. 57. butorphanol.ti,ab. 58. dezocine.ti,ab. 59. sufentanil.ti,ab. 60. ketobemidone.ti,ab. 61. or/25-60 62. 24 and 61 63. randomi?ed.ab. 64. placebo.ab. 65. randomly.ab. 66. trial.ab. 67. groups.ab. 68. RCT.ti,ab. 69. ("double-blind*" or "single-blind*").ti,ab. 70. exp Clinical Trials/ 71. or/63-70 72. 62 and 71	
5. CINAHL (EBSCOhost)	S1 (MH “Dementia+”) S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 (MH "Narcotics") S21 (MH "Analgesics, Opioid") S22 TX narcotic* S23 TX opioid*	June 2012: 162 June 2013: 13 June 2014: 23

(Continued)

	S24 TX morphine S25 (MH "Morphine") S26 TX buprenorphine S27 (MH "Buprenorphine") S28 TX codeine S29 codeine S30 (MH "Codeine") S31 TX Dextromoramide S32 TX diphenoxylate S33 (MH "Diphenoxylate") S34 TX dextropropoxyphene S35 TX propoxyphene S36 TX diamorphine S37 TX dihydrocodeine S38 TX alfentanil S39 TX fentanyl S40 TX remifentanil S41 TX meptazinol S42 TX methadone S43 TX nalbuphine S44 TX oxycodone S45 TX papaveretum S46 (MH "Opium") S47 TX pentazocine S48 TX meperidine S49 TX pethidine S50 TX phenazocine S51 TX hydrocodone S52 TX hydromorphone S53 TX levorphanol S54 TX oxymorphone S55 TX butorphanol S56 TX dezocine S57 TX sufentanil S58 TX ketobemidone S59 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 S60 S19 and S59 S61 TX placebo S62 TX randomly S63 TX trial S64 TX groups S65 (MH "Clinical Trials") S66 TX "double-blind*" OR "single-blind*" S67 S61 or S62 or S63 or S64 or S65 or S66 S68 S60 and S67	
6. CENTRAL (*The Cochrane Library* for June 2012 and June 2013 searches and CRSO for June 2014)	#1 MeSH descriptor Dementia explode all trees #2 MeSH descriptor Delirium, this term only #3 MeSH descriptor Wernicke Encephalopathy, this term only #4 MeSH descriptor Delirium, Dementia, Amnestic, Cognitive Disorders, this term only #5 dement* #6 alzheimer* #7 "lewy* bod*" #8 deliri* #9 "chronic cerebrovascular" #10 "organic brain disease" or "organic brain syndrome" #11 "normal pressure hydrocephalus" and "shunt*"	June 2012: 100 June 2013: 3 June 2014: 1

(Continued)

#12 "benign senescent forgetfulness"
#13 "cerebr* deteriorat*"
#14 "cerebral* insufficient*"
#15 "pick* disease"
#16 creutzfeldt or jcd or cjd
#17 huntington*
#18 binswanger*
#19 korsako*
#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR
#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 MeSH descriptor Narcotics explode all trees
#22 MeSH descriptor Analgesics, Opioid, this term only
#23 narcotic*
#24 opioid*
#25 morphine
#26 MeSH descriptor Morphine, this term only
#27 buprenorphine
#28 MeSH descriptor Buprenorphine, this term only
#29 codeine
#30 MeSH descriptor Codeine, this term only
#31 dextromoramide
#32 diphenoxylate
#33 MeSH descriptor Diphenoxylate, this term only
#34 dipipanone
#35 dextropropoxyphene
#36 MeSH descriptor Dextropropoxyphene, this term only
#37 propoxyphene
#38 diamorphine
#39 dihydrocodeine
#40 alfentanil
#41 fentanyl
#42 remifentanil
#43 meptazinol
#44 methadone
#45 MeSH descriptor Methadone, this term only
#46 nalbuphine
#47 oxycodone
#48 papaveretum
#49 MeSH descriptor Opium, this term only
#50 pentazocine
#51 MeSH descriptor Pentazocine, this term only
#52 meperidine
#53 pethidine
#54 phenazocine
#55 MeSH descriptor Phenazocine, this term only
#56 MeSH descriptor Hydrocodone, this term only
#57 hydrocodone
#58 MeSH descriptor Hydromorphone, this term only
#59 hydromorphone
#60 MeSH descriptor Levorphanol, this term only
#61 levorphanol
#62 oxymorphone
#63 MeSH descriptor Oxymorphone, this term only
#64 butorphanol
#65 MeSH descriptor Butorphanol, this term only
#66 dezocine
#67 sufentanil
#68 MeSH descriptor Sufentanil, this term only
#69 ketobemidone
#70(#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR

(Continued)

	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69) #71 (#20 AND #70) [2012-2013]	
7. LILACs (Bireme)	demenc$ OR dement$ OR vascular OR VCI OR Vad OR CADASIL OR multi-infarct OR binswanger OR alzheimer OR alzheimers [Words] and narcotic OR narcotics OR opiate OR opioid OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol OR methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone [Words] and placebo OR randomly OR randomised OR randomized OR "double-blind" OR "double-blinded" OR "control group" OR RCT [Words]	June 2012: 3 June 2013: 3 June 2014: 0
8. ClinicalTrials.gov	Interventional Studies | dementia OR alzheimers OR AD OR alzheimer's OR alzheimer OR lewy OR FTLD OR FLD | methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone OR narcotic OR opioid OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol	June 2012: 9 June 2013: 4 June 2014: 4
9. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	Advanced search: (dementia OR alzheimers OR alzheimer's OR alzheimer OR lewy OR FTLD) AND (methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone OR narcotic OR opioid OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol): recruitement status: ALL	June 2012: 4 June 2013: 0 June 2014: 0
10. Web of Science and Conference Proceedings	Topic=(dementia OR alzheimer* OR AD OR lewy OR memory OR CJD OR JCD OR creutzfeldt OR binswanger OR korsakoff OR aMCI) AND Topic=(narcotic* OR opioid* OR opium OR morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR propoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanil OR meptazinol OR methadone OR nalbuphine OR oxycodone OR papaveretum OR pentazocine OR meperidine OR pethidine OR phenazocine OR hydrocodone OR hydromorphone OR levorphanol OR oxymorphone OR butorphanol OR dezocine OR sufentanil OR ketobemidone) AND	June 2012: 416 June 2013: 66 June 2014: 42

(Continued)

	Topic=(randomised OR randomized OR randomly or placebo or "double-blind" or trial OR groups OR "controlled study" OR RCT OR "single-blind*") Timespan=All Years. Search language=English Lemmatization=On
Total pre-deduplication for all three searches	1892
Total after de-duplication	1077
Total after first assess based to title and abstract screen	50

CONTRIBUTIONS OF AUTHORS

The text and protocol were drafted by RB and ES with contributions from BC. ES, BC and RH reviewed and suggested amendments to the text during its drafting.

DECLARATIONS OF INTEREST

Richard Brown - None known
Robert Howard- None known
Bridget Candy- None known
Elizabeth L Sampson- None known

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Internal sources

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- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*therapeutic use]; Dementia [*psychology]; Psychomotor Agitation [*drug therapy]

MeSH check words

Humans