An integrative literature review exploring the clinical management of delirium in patients with advanced cancer

Lawley, Hayley ; Hewison, Alistair

DOI:
10.1111/jocn.13960

JCN Journal of Clinical Nursing

An integrative literature review exploring the clinical management of delirium in advanced cancer patients.

Journal:	*Journal of Clinical Nursing*
Manuscript ID	JCN-2017-0051.R2
Manuscript Type:	Review
Keywords:	Adult Nursing, Cancer, Death and Dying, End of Life Care, Management

[Type text]

An integrative literature review exploring the clinical management of delirium in patients with advanced cancer.

[Type text]

Abstract

Aim: The aim of this paper is to present the findings of an integrative literature review of the evidence for the clinical management of delirium in patients with advanced cancer.

Background: Patients with advanced cancer frequently experience delirium which can be distressing for both patients and their families. Current guidelines recommend that underlying causes of the delirium be addressed and a course of antipsychotics considered. However the research into the effectiveness of treatments for delirium in people with advanced cancer is limited.

Design: Integrative literature review

Data sources: Systematic searches of the MEDLINE, CINAHL, ProQuest Nursing and Allied Health and PsychInfo databases were conducted in April 2016 to include papers published in 2000 and later. The returns were screened using inclusion and exclusion criteria and the seven studies found to be suitable were subject to review.

Review Methods: Findings of the seven papers were extracted, appraised critically and reviewed using a narrative approach.

Results: A number of interventions, including the use of atypical antipsychotics, opioid rotation, methylphenidate hydrochloride and celiac plexus block were reported however there was limited evidence of their effectiveness. One study reported the use of exercise therapy as a non-pharmacological intervention.

Conclusion: A variety of interventions to treat delirium in patients with advanced cancer have been tested through non-blinded, non-randomised trials which has not produced a clear evidence-base for practice. There is a need for further research (particularly randomised control trials) to determine the most effective treatments for patients with advanced cancer experiencing delirium.

Key Words: literature review, delirium, palliative care, end of life, advanced cancer, neoplasm, management, nursing.

[Type text]

What does this paper contribute to the wider global clinical community?

Why is this review needed?

- There is a lack of evidence to inform the management of delirium in patients with advanced cancer. .
- The lack of evidence for the management of delirium in patients with advanced cancer means that patients, their families and carers, may not be receiving the most appropriate care.

Key Findings:

- Available research on the clinical management of delirium in advanced cancer is limited and of variable quality.
- A number of pharmacological and non-pharmacological interventions have been used to treat delirium in patients with advanced cancer however the evidence base for practice is limited.

How should these findings be used?

- These findings highlight the need for further investigation of the treatment of delirium in advanced cancer.
- Provide insights for nurses and other professionals on the effectiveness of the treatments currently in use.

[Type text]

The Review

Introduction

Patients with advanced cancer often experience delirium, yet strategies for its early detection, prevention, and management are limited (Caraceni and Simonetti 2009). Delirium is one of the most difficult syndromes to diagnose and treat and has an adverse impact on the quality of life for the patient and their family in the final days of life (Centeno et al 2004). There are various definitions of advanced cancer, however for the purpose of this paper, advanced cancer is that which cannot be cured and is likely to cause death (American Cancer Society, 2014). This means that End of Life concerns, such as preferred place of death, are real and valid for those diagnosed with advanced cancer. For example, although most people would prefer to die at home rather than in hospital (National Audit Office, 2008), delirium can result in longer hospital stays (Ljubisavljevic and Kelly, 2003), meaning patients may not be able to die in their preferred place. Moreover family members and carers generally provide the most care for their loved ones experiencing delirium which causes distress (Namba et al, 2007), which is often exacerbated as delirious patients are more likely to be non-compliant and risk putting themselves or others in danger (for example by pulling out IV lines/catheters) and being aggressive.

In view of this a need to examine the evidence for the clinical management of delirium in patients with advanced cancer was identified, in order to determine how it can be best managed. The aim of this review was to examine evidence for pharmacological and non-pharmacological treatments for delirium in patients with advanced cancer to determine the evidence base for practice and to highlight gaps in knowledge

[Type text]

Background

One of the most challenging aspects of end of life care, and a reason why many patients stay in and die hospital, is poor symptom control. Effective amelioration of symptoms including delirium, pain and nausea can help a patient to have a 'good death' (de Jong and Clarke, 2009). Although guidelines exist for the general and more specific management of delirium in cancer patients (NICE 2015, CCO 2010, Western Australia Cancer & Palliative Care Network 2010), the guidance concerning treatment in patients with advanced cancer is limited, in part because of the limited evidence available. The treatment and medication patients may receive as part of their cancer treatment can mean the standard approach to treating delirium is less effective.

Delirium is defined as a neurocognitive disorder characterised by a disturbance in attention and cognition, which can result from another medical condition (or from multiple aetiologies) for example pyrexia and malnutrition. The condition develops over a short period of time and cannot be explained by any another neurocognitive disorder (Diagnostic and Statistical Manual of Mental Disorders - V, 2013). Delirium can manifest in a number of ways (see table 1) and in practice, it is often nurses who recognise the symptoms when they first present. A variety of tools exist which can be used to help identify and diagnose the condition. For example the National Institute for Health and Care Excellence (NICE 2010) recommends the use of the Diagnostic and Statistical Manual of Mental Disorders – IV (DSM-IV) criteria or the Confusion Assessment Method (CAM), although other tools including the MDAS (Memorial Delirium Assessment Scale) and the MMSE (Mini-Mental State Examination) are available and often used in screening. Despite the availability of these tools however, the rate of detection of delirium in patients in practice is low. Ryan et al, 2013 found that nurses identified 63.6% of patients with delirium as confused or delirious,

[Type text]

however only 43.6% of those patients had the observation they were confused recorded in their notes. In a study of patents with advanced cancer it was found that the overall detection rate in patients with terminal cancer by any member of the palliative team was 44.9% and the detection rate of the hypoactive subtype was only 20.5%, significantly lower than that of the hyperactive/mixed subtypes (see below) (Fang et al 2008).

(Table 1 here)

Although the term delirium is widely used, there are distinct subtypes of delirium which are based on their clinical presentation. They are: hyperactive, hypoactive and mixed, and delirium with catatonic symptoms. For example, a comparison of symptoms of delirium in a range of patients found that 50.15% had the hyperactive subtype, 24.61% the mixed subtype and 19.93% the hypoactive subtype (Grover et al 2014). In other studies, the mixed type of delirium was most common (Peterson et al 2006; Kim et al 2015). Patients with hyperactive delirium are often restless, agitated and hyper-vigilant and experience perceptual disturbances and delusions, whereas patients with hypoactive delirium demonstrate lethargy and minimal spontaneous movement (Fang et al, 2009; Grover et al, 2014). The identification of different subtypes raises the issue of whether they should be treated as separate conditions, especially noting that patients experiencing hypoactive and mixed types of delirium have a poorer prognosis than those with hyperactive delirium (Kim et al, 2015), suggesting different treatment approaches may be needed.

Estimates for total cancer deaths in 2012 were 8.2 million (about 22,000 cancer deaths a day), and by 2030 the global burden is expected to grow to 21.7 million new cancer cases and 13 million cancer deaths (American Cancer Society 2015). The prevalence of delirium in patients with terminal cancer ranges from 28% to 85% (Minagawa et al 1996; de la Cruz et al, 2015; Massie et al 1983). This large variation may be a result of the difficulties involved

[Type text]

in accurately identifying the symptoms of the different subtypes of delirium (particularly hypoactive delirium), misdiagnosis, or a lack of the training staff need to make an assessment. Patients with cancer are at particular risk of developing delirium for a number of reasons, including exposure to certain drugs (opioids, corticosteroids, and benzodiazepines) (Gaudreau, 2005), and the presence of bone metastases and haematological malignancies (Ljubisavljevic and Kelly, 2003). In a recent literature review it was concluded that there needs to be a greater understanding of delirium in palliative care, including its pathophysiology and causation, as well as its treatment (Grassi et al 2015).

Current Clinical Management

Current approaches to the care of people with delirium involve non-pharmacological and pharmacological management. Non-pharmacological interventions are recommended such as nurses ensuring there is a clock visible in clinical areas and explaining to patients where they are and introducing themselves and other staff members, helping to keep patients orientated to time and place (NICE, 2010). Preventing precipitating factors such as constipation and dehydration can also help (NICE 2010), and this entails nursing staff planning care to ensure patients are mobilised, encouraged to drink and that bowel movements are monitored. Pharmacologically, the recommended initial treatment is a short term, low dose course of haloperidol or olanzapine. Hui et al (2010) for example found olanzapine was given to 17% of delirious patients and haloperidol to 72% of the patients, perhaps reflecting the evidence that Haloperidol has been shown to reduce symptoms of delirium in patients with cancer with no significant side effects (Akechi et al 1996). Delirium is also one of the most common reasons patients with advanced cancer are prescribed sedation (Alonso-Babarro et al, 2010;

[Type text]

Beller et al, 2014), which has been criticised on the basis that its use should be decided on an individual basis (National Ethics Committee, Veterans Health Administration, 2007).

The management of delirium requires an interdisciplinary approach (Milisen et al, 2001; Meagher, 2001) with nurses holding a key role in its prevention, detection and management (Siddiqi et al 2006), as they are at the front line of care and provide the majority of screening on admission to hospital. Tools available for nurses to use to identify the presence of delirium include the Mini-Mental State Exam (MMSE) which is comprised of five sections assessing orientation, registration, attention, recall and language. Its use has been effective in detecting delirium and as a diagnostic aid (Anthony 1982; Faught 2014). On the basis of the outcome nurses can refer patients to the appropriate healthcare professionals for further assessment and treatment.

Despite the increasing amount of research into delirium experienced at the end of life in the past decade (Close and Long, 2012; Harris, 2007), there are very few studies that focus on the treatment of delirium in patients with advanced cancer., A review of the evidence exploring the management of delirium in patients post-surgery and those being cared for in intensive care settings, found delirium can be improved in around half of patients by removing precipitating factors (Kang et al 2013). Although this highlights some useful evidence for practice, the study did not specifically address the needs of patients with advanced cancer, where it is often not possible to eliminate some of the precipitating factors identified. Patients who are at the end of their life as a result of advanced cancer are often receiving chemotherapy and opioid pain relief, which may mean the delirium experienced and the treatment for that delirium is different to that experienced by patients who do not have advanced cancer.

[Type text]

Design

The design of this study is an integrative literature review. The purpose of nursing research is to solve problems or answer questions that are relevant to nursing practice (Polit and Beck, 2014). The clinical management of delirium in patients with advanced cancer is one such problem. Although it is a common phenomenon (Minagawa et al 1996; de la Cruz et al, 2015; Massie et al 1983), there is little guidance in practice concerning how best to manage it. The review question was developed using the Population, Intervention and Outcome elements of the PICO model (Polit and Beck, 2014). This was used to guide the development of the question and because the focus was on studies reporting any intervention to alleviate delirium in patients with advanced cancer the C (comparator) element was not required. This process is summarised in Table 2.

(Table 2 here)

An initial search revealed there was little research reporting the treatment of delirium in patients with advanced cancer. Consequently although a systematic review is generally the recommended approach (Cullinan, 2005), it was not appropriate for this question because of the variety of interventions explored in the relevant literature. In view of this an integrative review was undertaken. In contrast to a systematic reviews, which aim to systematically search for, appraise and synthesise research evidence, aiming for exhaustive and comprehensive searching (Grant and Booth, 2009) and adhere to a strict design based on explicit, pre-specified, and reproducible methods (Gopalakrishnan and Ganeshkumar 2013) and generally focus on randomised controlled trials (Akenborg 2005), in an integrative of review, studies using diverse methodologies can be included and the approach has the potential to play a greater role in evidence-based practice for nursing (Whittemore and Knafl 2005). It is a review method which summarises previous empirical or theoretical literature, to

[Type text]

provide a more comprehensive understanding of a healthcare problem (Broome 1993 [cited in Whittemore and Knafl, 2005]). The primary sources included in an integrative review need to be logically grouped to facilitate analysis (Whittemore and Knafl, 2005). Ryan (2013) recommends that the similarities and differences of the findings of different studies and patterns in the data should be explored and in the review reported here there were interventions that could be considered together.

Search Methods

Four databases; MEDLINE, CINAHL, ProQuest Nursing and Allied Health and PsychInfo were searched because they were likely to include sources addressing the review question as they focus on medicine, nursing and psychology. The searches were conducted in April 2016 to include papers published in 2000 and later. Table 3 identifies the search terms used. The search terms were derived from the research question and the databases were searched using those key words or phrases identified. Boolean operators (AND, OR, NOT) were used to further refine the search. A 'wildcard' was also used, which allows multiple words to be searched for which have the same truncation, for example 'deliri*' would return results for 'delirium' and 'delirious' (Aveyard, 2010). One article was found through hand-searching through the reference lists of relevant articles (Horsely et al, 2001). Papers were excluded if they were unavailable in English, but not if they were conducted in other countries and reported in English. The inclusion and exclusion criteria used to determine the selection of papers for review are shown in Table 4.

(Table 3 here)

(Table 4 here).

[Type text]

Search Outcomes

The results of the screening process are shown in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) in figure 1 below. The selection of the papers for inclusion in the review was made following independent review of titles and abstracts by both authors. Titles and abstracts were identified by the systematic search of the databases noted earlier, guided by the application inclusion and exclusion criteria (Table 4). Papers found not to be relevant to the aims of study by their titles and abstracts were excluded. The full text versions of the twenty seven papers which met the inclusion criteria were obtained and read. On the basis of this second stage of independent review seven were found to be suitable for full critical review (see figure 1).

(Figure 1 here)

Data Abstraction

All the articles retrieved were read several times by one author and reviewed by the second author to gain a deeper understanding of the studies. A data abstraction form was used to record the key content of each paper in preparation for analysis (Polit and Beck, 2014). The design, aim sample, tool, results, limitations identified and recommendations made in the papers are summarised in table 5.

(Table 5 here)

Summary of the Studies included

Arai at al, 2013: This prospective study investigated terminal delirium in patients with pancreatic cancer and found that those who underwent a celiac plexus block had terminal delirium for a shorter time than those who did not.

[Type text]

Boettger and Breitbart, 2011: An open label naturally assigned study of patients with cancer (46.7% had advanced cancer) that investigated whether aripiprazole could be used to treat delirium. It found that aripiprazole may be safe and effective in treating delirium.

Moryl et al, 2005: Investigated 'switching' to methadone as part of an opioid rotation strategy in patients with advanced cancer and found that methadone may be considered in treating terminal delirium before the introduction of sedation.

Morita et al, 2005: Examined opioid rotation (morphine to fentanyl) in patients with cancer receiving palliative care who were experiencing morphine induced delirium, and found that the switch to fentanyl may alleviate the delirium.

Tatematsu et al, 2011: Investigated exercise therapy as an approach to reducing delirium in patients with cancer and found that the antipsychotic dose was lower in those in who received exercise therapy concluding that exercise therapy had potetntial as a non-pharmacological intervention for the management of delirium.

Gagnon et al, 2005: Investigated the use of methylphenidate in treating hypoactive delirium in patients with advanced cancer, finding that hypoactive delirium with no known aetiology may be improved by prescribing methylphenidate.

Breitbart et al, 2002: Demonstrated the efficacy and safety of olanzapine for use in the management of delirium patients with cancer in hospital.

Critical Appraisal

The articles were then subjected to critical appraisal which involved assessing the strengths and weaknesses of the selected papers in order to assess their relevance to the review question (Aveyard, 2010). The papers were reviewed to assess trustworthiness and quality using a set of recognised criteria (Mhaskar et al, 2009; Polit and Beck, 2014). The critical appraisal of the papers involved the use of a tool designed to assess the quality of

[Type text]

studies employing a quantitative design (Hek and Moule 2006), supplemented with key questions developed by Polit and Beck (2014). These were combined in an appraisal form which can been seen in figure 2.

(Figure 2 here).

The appraisal of the specific statistical tests used in the studies can be seen in table 6 (seen in the statistical analysis section below), and the overall quality ratings of the papers resulting from the application of the appraisal tool in figure 2 can be found in table 7.

(Table 7 here)

Synthesis

There is a lack of research which investigates delirium experienced by patients with advanced cancer and that which exists is of variable quality. No randomised control trials of interventions developed to treat delirium could be located. The review of the 7 articles suitable for inclusion demonstrated that a range of pharmacological and non-pharmacological interventions have been explored. It was not possible to combine and analyse the results using statistics because the papers investigated the use of different interventions using different methods. In view of this, the results are grouped on the basis of the main findings as a basis for further discussion of their implications. The common main findings were identified by reading through the included studies, identifying the types of interventions that were used and considering the implications of these approaches. The interventions identified were use of: atypical antipsychotics, opioid rotation, other pharmacological interventions and non-pharmacological interventions. However before considering these further, a number of general points about the studies are presented below.

[Type text]

Results

Design

All of the studies lacked the rigour of RCTs, as they were open-label, non-blinded and non-randomised (Sedgwick 2014), although most did report statistically significant results (apart from Moryl et al, 2005 which does not include any statistical analysis). All of the studies excepting Tatematsu et al (2011) were prospective in nature.

Sampling

The studies all used purposive sampling, a technique often used in qualitative research, where researchers select participants who can best address the purpose of the study (Aveyard, 2010). This type of sampling can introduce bias because of the absence of randomisation (Clifford, 1997). However in the studies reviewed here, the sample characteristics were so specific that it may have been difficult to recruit the patients in any other way. Excepting Breitbart et al (2002) sample sizes were less than 30 (the 2010 study by Tatematsu used 31 patients for the control group and 17 for the intervention group) which affects the statistical significance of the findings (Krithikadatta, 2014). Power calculations to determine the sample size required to test their hypothesis (Polit and Beck, 2014), were not carried out, (or were not reported on), in the seven studies.

Tools

A number of tools were used to collect data about the presence and severity of delirium. The MDAS was the commonest (Boettger and Breitbart 2011, Moryl et al 2005, Breitbart et al 2002). The Japanese version, which omits some the original items, was used by Morita et al (2005). The CAM, DOS and MMSE were used in other studies (Tatematsu et al 2011; Arai et al 2013; Gagnon et al 2005). The use of different tools means identification of delirium varied between the studies. Those using MDAS applied different thresholds for the definition

[Type text]

of delirium, for example Breitbart et al (2002), Boettger and Breitbart (2011) and Morita et al (2005) considered an MDAS < 10 to indicate delirium resolution, whereas a score of less than 13 is generally accepted as accurate (Alici and Breitbart, n.d).

Statistical Analysis

All of the papers include statistical analysis of the results (producing inferential statistics) apart from Moryl et al (2005), which includes descriptive statistics. The statistical test used depends on the type of data, whether it is parametric or non-parametric, and then the type of data generated; nominal, ordinal, interval or ratio. Parametric data follows a normal distribution (usually a sample of 30 or more is required for this) and non-parametric data does not follow normal distribution (Krithikadatta, 2014). A variety of statistical tests were used to analyse the data. Table 6 summarises the tests used and their appropriateness for the type of data they were analysing (Institute for Digital Research and Education, n.d.).

(Table 6 here)

Main Treatment Approaches

Atypical Antipsychotics

The use of atypical antipsychotics was explored in two of the papers, olanzapine (Breitbart et al 2002) and aripiprazole (Boettger and Breitbart 2011). Both report statistically significant results, with Boettger and Breitbart (2011) recording the mean MDAS at T1 was 18.0 which reduced to a mean MDAS at a stable dose of aripiprazole at T3 of 8.3 ($p < 0.001$). Breitbart et al (2002) found 76% of the patients had resolution of their delirium at T3 based on an MDAS of < 10, meaning the MDAS score improved from 19.85 (± 3.79) to 10.78 (± 7.31), $P = 0.001$. The statistical significance of these findings needs to be treated with caution because of the open-label non-randomised study designs. For example Breitbart et al (2002)

analysed confounding factors and found that treatment outcome was affected by designation of the delirium subtype. This suggests that the management of subtypes could be different.

Opioid Rotation

Two studies explored opioid rotation in the management of delirium. The change to Methadone for patients with morphine induced delirium (Moryl et al, 2005), and the replacement of morphine with Fentanyl (Morita et al, 2005). Moryl et al (2005) found 'average' MDAS improved from 23.6 to 10.6, but it is not specified if this is referring to the mean, mode, or median. When Fentanyl was introduced the mean MDAS decreased from 14 at T1 to 3.6 at T3 ($p < 0.001$) (Morita et al 2005). However, the tool used to collect this data was the Japanese version of the MDAS, with some of the original items excluded, so again the results need to be regarded with caution.

Other Pharmacological Interventions

Two studies reporting other pharmacological interventions were located. The first investigated the use of a Celiac Plexus Block (CPB), and it was found that the duration of Terminal Delirium (TD) was lower in the CPB group than the control group (1.8 ± 2.9 vs 10.4 ± 7.5 days respectively) (Arai et al, 2013). In the second Methylphenidate hydrochloride (Gagnon et al 2005) was prescribed for patients with hypoactive delirium resulting in an improvement from 20.9 ± 4.9 pre-treatment to 27.8 ± 2.4 on the MMSE when the patients were on a stable dose of methylphenidate (Gagnon et al 2005). Its use for the treatment of hypoactive delirium in the study limits its generalisability to other forms of delirium.

Non-Pharmacological Intervention

[Type text]

The only report of a non-pharmacological intervention located, investigated the use of exercise therapy (Tatematsu et al, 2011). It found that antipsychotic dose was lower in the experimental group (2.198mg) than the control group (5.533mg) ($P < 0.036$),however the sample size was too small for the results to be generalizable. This study indicates there may be potential in non-pharmacological interventions as a wider range of staff would be able to deliver them.

Discussion

The findings of the research demonstrate that although there has been some investigation of the treatment of delirium in patients with advanced cancer, relatively few rigorous studies have been conducted. In terms of pharmacological interventions, the use of atypical antipsychotics reduced mean MDAS scores (Boettger and Breitbart, 2011; Breitbart et al, 2002), as did opioid rotation (Moryl et al, 2005 and Morita et al, 2005), a celiac plexus block reduced the duration of terminal delirium (Arai et al, 2013), and methylphenidate was found to be effective in patients with hypoactive delirium (Gagon et al, 2005). The one report of a non-pharmacological intervention found that the dose of antipsychotics could be reduced for patients participating in exercise therapy (Tatematsu et al, 2011).

The findings of this literature review are inconclusive in terms of identifying a single safe and effective treatment for delirium experienced by patients with advanced cancer. Haloperidol is often the first line treatment for delirium (NICE, 2010), however, a conference paper identified in the literature search reported that haloperidol alone was insufficient to control delirium in patients with advanced cancer because while 128 of the 167 patients required therapy with only haloperidol, 39 required a second neuroleptic to control symptoms (Susman, 2014).

Another first line treatment for delirium is olanzapine, which Breitbart et al (2002) investigated and even though the rigour of the study is not comparable with an RCT, the

results were still deemed to be significant. The use of aripiprazole has not been explored to a great extent although small studies such as the one by Boettger and Breitbart (2011) indicate it has helped resolve delirium. Further work is needed to determine if it can be added to the drugs licenced to treat delirium.

The substitution of one opioid for another can improve therapeutic response and/or reduce side effects (Moryl et al 2005; Morita et al 2005; Knotkova et al, 2009). Cancer patients often experience pain and are prescribed opioids for pain relief even though this increases the risk of delirium (Gaudreau et al, 2007; Morrison et al 2003). Further investigation of the effects of opioid rotation is important for the treatment of delirium in patients with advanced cancer. The final pharmacological intervention studied was the use of methylphenidate hydrochloride in patients with hypoactive delirium (Gagnon et al, 2005). Methylphenidate is licenced to treat attention-deficit hyperactivity disorder (ADHD) (BNF, 2014). It works by increasing the amount of dopamine available in areas of the brain responsible for reward and motivation (Volkow et al, 2012) and causes a 'calming' effect on patients with ADHD. Because the pathophysiology of delirium is still not fully understood (Bush and Bruera 2009), it is not clear how methylphenidate works to improve symptoms. This suggests further trials of this agent would be of value.

The one non-pharmacological intervention studied was exercise therapy (Tatematsu et al, 2011), which was found to be a useful adjunct to pharmacological treatment in mental health settings and is of relatively low cost (Daley, 2002). Studies which explore non-pharmacological interventions are of particular interest to nurses, because if they are proven to be effective, they can be readily incorporated into the nursing management of patients with delirium. They are also useful because they can be investigated without the concomitant risk of adverse effects such as side effects or serious complications, anaphylactic shock for example, that can occur with pharmacological interventions (Cancer Research UK, 2015).

[Type text]

There remains limited information from randomised controlled trials of pharmacological agents to guide practice in evidence-based neuroleptic administration to cancer and palliative care patients (Bush and Bruera 2009). Further research is needed to determine efficacious and safe drugs and dosages for the different delirium subtypes and aetiologies, as well as the role of nonpharmacological and environment management strategies in improving improve the comprehensive multifaceted management of this distressing syndrome (Bush and Bruera 2009).

With regard to the implications of the findings for clinical practice it is important to consider options available to alleviate the distressing symptoms of delirium. Although treatments unlicensed for use in delirium such as aripiprazole and olanzapine cannot be introduced, interventions including exercise therapy could be considered. Also the findings suggest that initiating discussions with doctors and pharmacists about the potential of opioid rotation is worthy of further exploration. In addition practicing in accordance with current guidelines for the care and treatment of delirium, including the provision of aides to orientation (for example having clocks and calendars visible in clinical areas), should remain a priority of care (NICE 2010).

Limitations

As with any literature review this one has limitations. For example, unpublished or 'grey' literature was not included which has the potential to introduce publication bias, in that journals tend to favour articles which report positive results, leading to over-representation of significant findings (Cullinan, 2005; Polit and Beck, 2014). Also in view of the type of interventions used in the treatment of delirium the nature of the studies reported varied, an integrated approach was taken because a meta-analysis was not possible.

[Type text]

Conclusion

Delirium is a poorly understood condition which is frequently experienced by patients with advanced cancer, however there is limited knowledge of its pathophysiology, particularly of its subtypes. The findings from the seven studies examined in this review do not provide a conclusive evidence base for the treatment of delirium for patients with advanced cancer, although the interventions seemed to have some impact in terms of reducing the severity or the duration of the delirium.

However despite the lack of evidence on which to make definitive recommendations about treatment and care the current gap in knowledge has been identified, and there appear to be some promising areas for further research. More work is needed to build understanding of the pathophysiology of delirium in patients with advanced cancer and once this is more widely understood there can be more informed research into its treatment. Ideally this should take the form of Randomised Controlled Trials that can take account of confounding factors including age, co-treatments and cancer diagnosis (stage and tumour site) so that the effect of these factors can be analysed, so the true reason for delirium resolution can be identified.

[Type text]

References

Agency for Health Care Research and Quality (2011) Palliative care for the patient with incurable cancer or advanced disease. Part 2: pain and symptom management. Available at https://www.guideline.gov/summaries/summary/38885/palliative-care-for-the-patient-with-incurable-cancer-or-advanced-disease-part-2-pain-and-symptom-management Accessed 4th August 2016.

Akechi T., Uchitomi Y., Okamura H., Fukue M., Kagaya A., Nishida A., Oomori N., Yamawaki S. 1996. Usage of haloperidol for delirium in cancer patients. *Supportive Care in Cancer*. 4:390-392.

Akobeng A.K. (2005) Principles of evidence based medicine. *Archive of Diseases in Childhood* 90, 837-840.

Alici Y., Breitbart W., n.d. MDAS. Encyclopedia of psycho-pharmacology [online]. Available at: http://download.springer.com/static/pdf/325/prt%253A978-3-540-68706-1%252F13.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Freferenceworkentry%2F10.1007%2F978-3-540-68706-1_1159&token2=exp=1470056650~acl=%2Fstatic%2Fpdf%2F325%2Fprt%25253A978-3-540-68706-1%25252F13.pdf%3ForiginUrl%3Dhttp%253A%252F%252Flink.springer.com%252Freferenceworkentry%252F10.1007%252F978-3-540-68706-1_1159*~hmac=85c0c3880267abb98ef947d7a78b3604765f4fcb86c8e8e06539f35c4c6190de [Accessed 01/08/16].

Alao A.O., and Moskowitz L., 2006. Aripiprazole and delirium. *Annals of Clinical Psychiatry* 18(4):267-9.

Alonso-Babarro, M. Varela-Cerdeira, I. Torres-Vigil, R. Rodriguez-Barrientos, E. Bruera, 2010. At-home palliative sedation for end-of-life cancer patients. Palliative Medicine, 24:5 pp. 486–492

American Cancer Society, 2014. What is advanced cancer? Available at: http://www.cancer.org/treatment/understandingyourdiagnosis/advancedcancer/advanced-cancer-what-is [Accessed 18/10/16].

American Cancer Society. (2015). *Global Cancer Facts & Figures* (Third Edition) Edition. American Cancer Society, Atlanta.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-V* [online]. Available at: http://reader.eblib.com/(S(xstn1pgsjtq1mnsvb4lplfce))/Reader.aspx# [Accessed 03/03/15].

Anthony J.C., LeResche L., Niaz U., Von Korff M.R., and Folstein M.F., (1982). Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. *Psychological Medicine*, 12:2, pp 397-408.

[Type text]

Arai Y-C. P., Nishihara M., Kobayashi K., Kanazawa T., Hayashi N., Tohyama Y., Nishida K., Arakawa M., Suzuki C., Kinoshita A., Kondo M., Masturbara S., Yokoe N., Hayashi R., Ohta A., Sato J., Ushida T., 2013. Neurolytic celiac plexus block reduces occurrence and duration of terminal delirium in patients with pancreatic cancer. *Japanese Society of Anaesthesiologists.* 27:1 p 88 – 92.

Averyard H., 2010. *Doing a Literature Review in Health and social care; a practical guide.* 3rd edition. Berkshire; Open University Press.

Bekelman J.E., Halpern S.D., Blankart C.R., Bynum J.P., Cohen J., Fowler R., Kaasa S., Kwietniewski L., Melberg H.O., Onwuteaka-Philipsen B., Oosterveld-Vlug M., Pring A., Schreyögg J., Ulrich C.M., Verne J., Wunsch H., Emanuel E.J. Comparison of Site of Death, Health Care Utilization, and Hospital Expenditures for Patients Dying With Cancer in 7 Developed Countries. *JAMA*. 19;315(3):272-83.

Beller E.M., van Driel M.L., McGregor L., Truong S., Mitchell G., 2014. Palliative pharmacological sedation for terminally ill adults. The Cochrane Library [online]. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010206.pub2/abstract;jsessionid=18B5F99B1C059A767E0D25E110F473CB.f02t02. Accessed 01/08/16.

Bettany-Saltikov J., 2012. How to do a systematic Literature Review in Nursing: A step-by-step guide. New York; Open University Press.

BNF, 2014. *Methylphenidate hydrochloride* [online]. Available at: https://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/44-cns-stimulants-and-drugs-used-for-attention-deficit-hyperactivity-disorder/methylphenidate-hydrochloride [Accessed 08/03/16].

Boettger S., Breitbart W., 2011. An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. *Palliative and Supportive Care*. 9:4 pp 351-357

Breitbart W., Tremblay A., Gibson C., 2002. An Open Trial of Olanzapine for the Treatment of Delirium in Hospitalized Cancer Patients. Psychosomatics. 43:3 p 175–182.

Bush S.H., and Bruera E. (2009). The assessment and management of delirium in cancer patients. The Oncologist 14 (10), 1039-1049.

Cancer Care Ontario (CCO)(2010) Cancer Care Ontario's Symptom Management Guide-to-Practice: Delirium. Available at: https://www.cancercare.on.ca/CCO_DrugFormulary/Pages/FileContent.aspx *(accessed 4th August 2016)*

Cancer Research UK (2015) Advantages & drawbacks of taking part in a clinical trial Available at: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-you-should-be-told-about-a-clinical-trial/advantages-and-drawbacks#C6cDTBRg3CYmJI7o.99 (accessed 4th August 2016)

Caraceni, A. and Simonetti, F. (2009) Palliating delirium in patients with cancer. The Lancet Oncology 10, 164-72.

Centeno C,, Bruera E. and Sanz, Á. (2004) Delirium in advanced cancer patients. Palliative Medicine 18, 184-194.

[Type text]

Clifford C., 1997. Nursing and Health Care Research: A skills-based Introduction. Hertfordshire; Prentice Hall Europe.

Close J.F, and Long C.O., Delirium: Opportunity for Comfort in Palliative Care. Journal of Hospice and Palliative Nursing. 14:6 pp386-394

Cullinan P., 2005. Evidence-based healthcare: systematic reviews. In: Bowling A., and Ebrahim S., eds 2005. *Handbook of Health Research Methods; Investigation, Measurement and Analysis*. England; Open University Press.

Daley A.J., 2002. Exercise therapy and mental health in clinical populations: is exercise therapy a worthwhile intervention? *Advances in Psychiatric Treatment*. 8:4 p 262-270

de Jong, J.D; Clarke L.E, 2009. What Is a Good Death? Stories from Palliative Care. *Journal of Palliative Care*. 25:1 PP. 61-7.

de la Cruz M; Noguera A; San Miguel-Arregui MT; Williams J; Chisholm G; Bruera E, 2015. Delirium, agitation, and symptom distress within the final seven days of life among cancer patients receiving hospice care. *Palliative & Supportive Care*. 13:2 p211-216.

Fang C-K., Chen H-W., Liu S.I., Lin C-J., Tsai L-Y., and Lai y-l. 2008. Prevalence, Detection and Treatment of Delirium in Terminal Cancer Inpatients: A Prospective Survey. *Japanese Journal of Clinical Oncology* 38(1)56–63.

Faught, D,D., 2014. Delirium: The Nurse's Role in Prevention, Diagnosis, and Treatment. *Medsurg Nursing* 23:5 301-305.

Fong, T. G., Tulebaev, S. R., Inouye, S. K., 2009. Delirium in elderly adults: diagnosis, prevention and treatment. *Nature Reviews. Neurology*, 5(4), 210–220.

Gagnon B., Graeme L., Schreier G., 2005. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. *Journal of Psychiatry and Neurosciences*. 30:2 p 100 – 107.

Gaudreau J.D., Gagnon P., Roy M.A., Harel F., Tremblay A. 2007. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. *Cancer*. 109(11):2365-73

Gaudreau J-D., Gagnon P., Harel F., Roy M-A., Tremblay A., 2005. Psychoactive Medications and Risk of Delirium in Hospitalized Cancer Patients. *American Society of Clinical Oncology*. 23:27 pp6712-6718.

Gopalakrishnan S. and Ganeshkumar P. (2013) Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. *Journal of Family Medicine and Primary Care* 2 (1), 9-14.

Grant M.J., Booth A., 2009. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Information and Libraries Journal*. 26: pp.91–108

Grassi L., Caraceni A.,, Mitchell A.J, Nanni M.G., Berardi M.A., Caruso R., Riba M., 2015 *Management of delirium in palliative care: a review.* Current Psychiatry reports 17 (13) pp 550.

[Type text]

Grover S., Sharma A., Aggarwal M., Mattoo S.K, Chakrabarti S., Malhotra S., Avasthi A., Kulhara P., and Basu D., 2014. Comparison of symptoms of delirium across various motoric subtypes. *Psychiatry and Clinical Neurosciences*. 68: 283–291

Harris D., 2007. *Delirium in advanced disease. Postgraduate Medical Journal*. 83(982): 525–528.

Hek G., and Moule P., 2006. *Making sense of research; an introduction for health and social care practitioners.* 3rd edition. London; SAGE publication ltd.

Horsley T., Dingwall O., Sampson M. 2011. Checking reference lists to find additional studies for systematic reviews. *Cochrane Database of Systematic Reviews*. 10:8.

Hui D., Bush S.H., Gallo L.E., Palmer J.L., Yennurajalingam S., and Bruera E., 2010. Neuroleptic dose in the management of delirium in advanced cancer patients. *Journal of pain and symptom management.* 39:2 186 – 196.

Husebo B.S., Ballard C., Sandvik, R, Nilsen O.B, Aarsland D, 2011. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *British Medical Journal*. 343.

Institute for Digital Research and Education, n.d. *What statistical Analysis Should I Use*? [online]. Available at http://www.ats.ucla.edu/stat/sas/whatstat/ [Accessed 02/02/16].

Kang J.H., Shin S.H., Bruera E. 2013. Comprehensive approaches to managing delirium in patients with advanced cancer. *Cancer Treatment Reviews*. 39(1):105-12.

Kennedy JS, Jeste D, Kaiser CJ, Golshan S, Maguire GA, Tollefson G, Sanger T, Bymaster FP, Kinon BJ, Dossenbach M, Gilmore JA, Breier A., 2003. Olanzapine vs haloperidol in geriatric schizophrenia: analysis of data from a double-blind controlled trial. *International Journal of Geriatric Psychiatry*. 18(11):1013-20.

Kim S-Y., Kim S-W., Kim J-M., Shin I-S., Bae K-Y., Shim, H-J., Bae, W-K., Cho S-H., Chung I-J., Yoon J-S., 2015. Differential Associations between Delirium and Mortality According to Delirium Subtype and Age: A Prospective Cohort Study. *Psychosomatic Medicine*. 77:8. p 903–910.

Knotkova H., Fine .PG., Portenoy R.K., 2009. Opioid rotation: the science and the limitations of the equianalgesic dose table. *Journal of Pain and Symptom Management* 38(3): p426-39.

Krithikadatta J., 2014. Normal Distribution. *Journal of Conservative Dentistry*. 17(1): 96–97.

Ljubisavljevic V., Kelly B., 2003. Risk factors for development of delirium among oncology patients. *General Hospital Psychiatry* 25:5 pp 345- 352.

Massie MJ, Holland J, Glass E., 1983. Delirium in terminally ill cancer patients. *American Journal of Psychiatry* 140:8 1048–1050

Meagher D.J., 2001. Delirium: Optimising Management. *British Medical Journal*. 322:114

[Type text]

Meier D.E., 2012. Pain as a Cause of Agitated Delirium. *Journal of the American Medical Association*. 172:15 p 1130.

Mhaskar R., Emmanuel P, Mishra S, Patel S., Naik E., Kumar A., 2009. Critical appraisal skills are essential to informed decision-making. *Indian Journal of Sexually Transmitted Diseases.* 30(2): 112–119.

Milisen, K., Foreman, M. D., Abraham, I. L., De Geest, S., Godderis, J., Vandermeulen, E., Fischler, B., Delooz, H. H., Spiessens, B. and Broos, P. L. O. (2001), A Nurse-Led Interdisciplinary Intervention Program for Delirium in Elderly Hip-Fracture Patients. *Journal of the American Geriatrics Society*, 49:5 p 523–532

Minagawa H., Uchitomi Y., Yamawaki S., Ishitani K., 1996. Psychiatric Morbidity in Terminally 111 Cancer Patients: A Prospective Study. *Cancer.* 78: 5 p 1131 – 1137.

Moher, D., Liberati, A., Tetzlaff, J. and Altman, D.G. (2009) *Preferred Reporting for systematic reviews and meta-analysis: The PRISMA Statement* [online]. http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000097 [Accessed 30/01/2016]

Morita T., Takigawa C., Onishi H., Tajima T., Tani K., Matsubara T., Miyoshi M, Ikenaga M., Akechi T, and Uchitomi Y., 2005. Opioid Rotation from Morphine to Fentanyl in Delirious Cancer Patients: An Open-Label Trial. *Journal of Pain and Symptom Management.* 30:1 p 96 - 103

Morrison R.S., Magaziner J., Gilbert M., Koval K.J., McLaughlin M.A., Orosz G., Strauss E., and Siu A.L., 2003. Relationship Between Pain and Opioid Analgesics on the Development of Delirium Following Hip Fracture. *Journal of Gerontology*. 58:1, P 76–78

Moryl N., Kogan M., Comfort C., Obbens E., 2005. Methadone in the treatment pf pain and terminal delirium in advanced cancer patients. *Palliative and Supportive Care*. 3:4 p 311-317.

Namba M, Morita T, Imura C, Kiyohara E, Ishikawa S, Hirai K, 2007. Terminal delirium: families' experience. *Journal of Palliative Medicine*. 21(7):587-94

National Audit Office, 2008. *End of Life care* [online]. Available at https://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf [Accessed 04/03/16].

National Ethics Committee, Veterans Health Administration, 2007. The Ethics of Palliative Sedation as a Therapy of Last Resort. American Journal of Hospice & Palliative Medicine. 23:6 pp 483-491.

NICE, 2010. *Delirium: prevention, diagnosis and management [CG103]* [online]. Available at: https://www.nice.org.uk/guidance/cg103 [Accessed 07/03/16].

NICE, 2015. Care of dying adults in the last days of life [NG31] [online]. Available at: https://www.nice.org.uk/guidance/ng31/chapter/Recommendations [Accessed 25/07/16].

[Type text]

Peterson J.F, Pun B.T, Dittus R.S, Thomason J.W.W., Jackson J.C., Shintani A.K., Ely E.W.,2006. Delirium and Its Motoric Subtypes: A Study of 614 Critically Ill Patients. The *Jo urnal of the American Geriatrics Society*. 54: 3 pp 479 – 484.

Polit D.F., and Beck C.T., 2014. *Essentials of Nursing Research: Appraising Evidence for Nursing Practice*. 8th edition. London: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Ryan D.J., O'Regan N.A., Ó Caoimh R., Clare J., O'Connor M, Leonard M., McFarland J., Tighe S, O'Sullivan K, Trzepacz P.T., Meagher D., Timmons S., 2012. Delirium in an adult acute hospital population: predictors, prevalence and detection. *BMJ Open.* 3:1.

Ryan R; Cochrane Consumers and Communication Review Group. 'Cochrane Consumers and Communication Review Group: data synthesis and analysis'. http://cccrg.cochrane.org, June 2013 (accessed 02/03/2017).

Sedgwick P. (2014) What is an open label trial? British Medical Journal 348:g3434 doi: 10.1136/bmj.g3434.

Siddiqi N., House A.O., and Holmes J.D., 2006. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age and Ageing*. 35 (4):350-364.

Susman E., 2014. Haloperidol alone found sufficient to control delirium in advanced cancer patients. *Oncology times* 36:15 pp 20-20.

Tatematsu N., Hayashi A., Narita K., Tamaki A., Tsuboyama T., 2001. The effect of exercise therapy on delirium in cancer patients: a retrospective study. *Supportive Care in Cancer.* 19:6 p 765 – 770.

The Economist Intelligence Unit, 2010. *The quality of death: Ranking end-of-life care across the world* [online]. Available at http://graphics.eiu.com/upload/eb/qualityofdeath.pdf [accessed 04/03/15].

Volkow N. D., Wang, G.-J., Tomasi, D., Kollins, S.H., Wigal, T.L., Newcorn, J.H., Telang, F.W., Fowler, J.S., Logan, J., Wong, C.T., Swanson, J.M., 2012. Methylphenidate-Elicited Dopamine Increases in Ventral Striatum Are Associated with Long-Term Symptom Improvement in Adults with Attention Deficit Hyperactivity Disorder. *Journal of Neuroscience.* .32(3) 841-849.

Western Australia Cancer & Palliative Care Network (2010) Evidence based clinical guidelines for adults in the terminal phase, Palliative Care for People Living at Home Initiative. Government of Western Australia, Department of Health. Available at: http://www.healthnetworks.health.wa.gov.au/cancer/docs/Evidenced_based_guidelines_flipbook.pdf (accessed 4th August 2016)

Whittemore R., and Knafl K, 2005. Methodological issues in nursing research: The integrative review: Updated Methodology. *Journal of Advanced Nursing*. 52:5. 546

Table 1: Symptoms of delirium by subtype.

Delirium Subtype	Symptoms
Hyperactive	Restlessness Agitation Hallucinations Delusions
Hypoactive	Lethargy Minimal spontaneous movement Slow in responding to questions Thought process abnormality
Mixed	A combination of hyperactive and hypoactive symptoms.

Table 2: Research Question Formulation, PIO

Population	Patients with advanced cancer
Interventions	Pharmacological and non-pharmacological treatments of delirium
Outcome	The management of delirium; whether the interventions improve, worsen or result in no change to delirium symptoms.

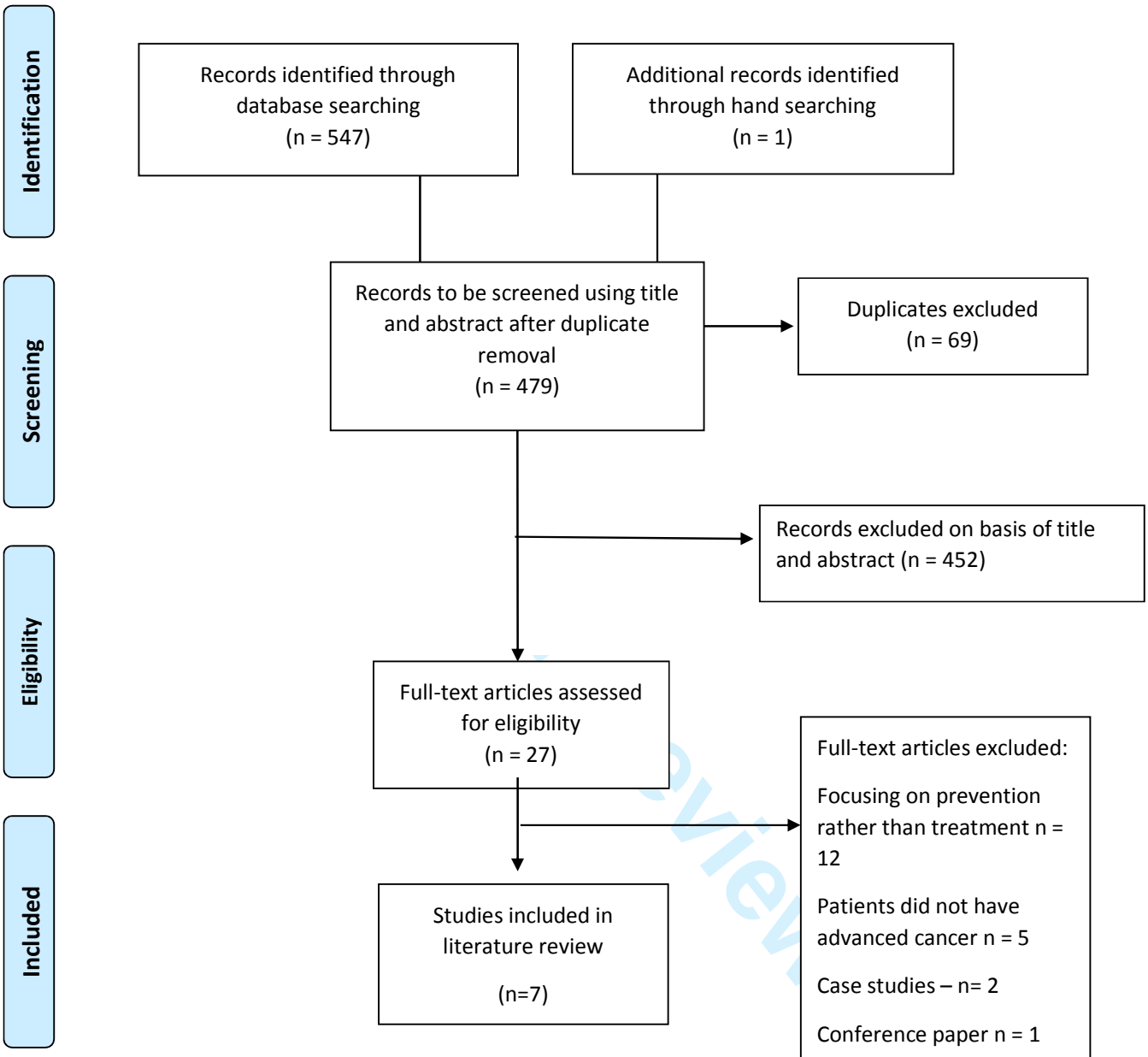
Table 3: Database Search Terms

Population	Population	Intervention	Outcome
Oncology	Supportive	Treatment	Deliri*
Cancer	"end of life"	Management	
Neoplasms	Palliative	Therapeutics	"acute confusion"

Table 4: Inclusion and exclusion criteria and rationale

Inclusion Criteria	Rationale
Patients with advanced cancer must make up the full or partial sample group	The research question focuses on advanced cancer patients, studies on those wither without cancer or cancer that is not advanced
Primary research	Less chance of bias than with secondary research.
Treatment of delirium must be the main focus of the article	The article must focus on treatment of delirium (treatment can be pharmacological or non-pharmacological) rather than prevention to address the research question
Exclusion Criteria	**Rationale**
Studies published before the year 2000	The studies are less likely to be relevant to todays practice
Secondary research	More chance of bias
Case Reports	The lack of generalisability was viewed as too great as the cases were often very complex.
Unpublished/grey literature	The researcher is novice and has limited time to search for data
Studies not published in English	The researcher is novice and only speaks fluent English, so does not have the time or resources to translate the articles.

Figure 1: PRISMA (adapted from Moher et al, 2009)



Paper	Design	Sample & Setting	Intervention	Delirium Screening tool(s)	Are tools reliable?	Analysis	Results	Conclusion
Boettger and Breitbart, 2011	Open Label Naturally Assigned prospective	N = 21 46.7% had advanced cancer Memorial Sloan-Kettering Cancer Centre – US	Aripiprazole	MDAS	Yes	Freidman	P < 0.001 mean MDAS T1 = 18.0, mean MDAS T3 = 8.3	Aripiprazole may be safe and effective in treating delirium.
Moryl et al, 2005	Open Label, prospective	N = 20 Advanced cancer patients. Tertiary cancer palliative care hospital -US	Methadone 'switch'	MDAS	Yes	None	'Average' MDAS. Improved from 23.6 to 10.6	A switch to methadone may be considered before sedation
Morita et al, 2005	Open Label Prospective	N = 21 Palliative Care patients, morphine induced delirium 7 palliative care units - Japan	Opioid Rotation; morphine to fentanyl.	MDAS (Japanese version). Omitted items	Original – yes Modified - no	Freidman	P < 0.001. Mean MDAS decreased from 14 at T1 to 3.6 at T3	Opioid Rotation; morphine to fentanyl may be effective in alleviating morphine induced delirium
Tatematsu et al, 2011	Open- label Retrospective	N = 48, EG = 17 NG = 31. Prognosis < 6 months' survival in EG = 35.5%; NG=41.9%. Kyoto University Hospital – Japan	Exercise therapy	CAM	Yes	Students t test	P < 0.036. Antipsychotic dose lower in EG (2.198mg) than NG (5.533mg).	Exercise therapy could be as an environmental intervention for delirium
Arai et al, 2013	Open-label Prospective CPB group,	N = 36 Control Group N = 17 CPB Group N = 19. Pancreatic cancer. TD. Palliative-care team - Japan	Neuroleptic Celiac Plexus Block	DOS	Yes	Unclear	P < 0.003. Duration of TD lower in CPB than control (1.8 ± 2.9 vs 10.4 ± 7.5 days respectively).	Duration of TD significantly less in patients who underwent CPB
Gagnon et al, 2005.	Open-label Prospective	N= 14 hypoactive delirium, advanced cancer. Montreal General Hospital – Canada.	Methylphenidate hydrochloride	MMSE	Yes	Wilcoxon signed rank test	P<0.001. Pre-treatment MMSE mean=20.9 ± 4.9, stable treatment MMSE mean=27.8±2.4	Hypoactive delirium with no known aetiology may be improved by methylphenidate
Breitbart et al, 2002	Open-Label, prospective	N = 79 Stage: terminal = 5%,. Memorial Sloan-Kettering Cancer - US	Olanzapine	MDAS	Yes	ANOVA	MDAS score improved from a mean of 19.85 to 10.78, P = 0.001. Subtype can affect outcome. 76% delirium resolution.	Study begins to demonstrate the efficacy and safety of olanzapine for use in the management of delirium among hospitalized medically ill patients

Table 5: Summary of Papers

Abbreviations;

MDAS = Memorial Delirium Assessment Scale
MMSE = Mini-Mental State Examination.
DOS =Delirium Observation Screening Scale
ANOVA = Analysis of variance
CAM = Confusion Assessment Method
T1 = Time 1; baseline measurement
T3 = Time 3; 4-7 days after intervention
± = standard deviation
TD = Terminal Delirium
N = number of participants
EG = Exercise Group
NG = Non-exercise group
CPB = celiac plexus block

Figure 2 - Critical Appraisal Tool

Abstract	Are key elements included? Are the Aims clearly stated?
Literature Review	Is the literature review up to date? Does the literature review establish a focus for the study due to a gap in knowledge?
Method: Research Design	Was the most rigorous possible deign used? Was bias minimised? Were the researchers blinded? Were the participants randomised?
Population and sample	Was the population identified and described? Was the best possible sampling design used to enhance the samples representativeness? Was the sample size adequate? Was sample bias present? Was there a control group? Were the inclusion/exclusion criteria stated?
Data collection and Measurement	Are the tools used adequately described and was it properly implemented? Does the report provide evidence that the data collection methods yielded data high on reliability and validity? Was data collected in a manner that minimised bias?
Procedures	If there was an intervention was it clearly described and properly implemented? Did most participants allocated to the intervention group receive it?
Results: Data Analysis	Were appropriate statistical methods used? Was $p < 0.05$? Did the analysis control for confounding variables?
Findings/Conclusions	Was information about statistical significance presented? Are limitations identified and discussed? Are the results generalizable? Does the researcher discuss the results in context of the previous literature? Does the researcher suggest implications for practice and further research?

Adapted from

Polit D.F., and Beck C.T., 2014. Essentials of Nursing Research: Appraising Evidence for Nursing Practice 8th edition. London: Wolters Kluwer Health/Lippincott Williams & Wilkins

And

Hek G., and Moule P., 2006. Making sense of research; an introduction for health and social care practitioners. 3rd edition. London; SAGE publication ltd.

Table 6: Statistical tests used

Article	Data	Normal Distribution	Type of Data	Statistical Test Used	Was the test appropriate?
Moryl, 2005	Change in MDAS score	No	Interval	None Used	N/A
Morita, 2005	Change in MDAS score	No	Interval	Friedman	Yes
Tatematsu, 2010	Difference in antipsychotic dose	Unclear	Ratio	Students t test	Unclear
Arai et al, 2013	Duration of terminal delirium	No	Interval	Unclear	Unclear
Boettger and Breitbart, 2011	Change in MDAS score	No	Interval	Friedman	Yes
Gagnon, 2005	Change in MMSE score	No	Interval	Matched-paired Wilcoxon signed rank test	Yes
Breitbart, 2002.	Change in MDAS score	Yes	Interval	ANOVA	Yes

Table 7 - Results of the Quality Appraisal

Article	Design (n/5)	Sample/Sampling (n/5)	Tools (n/5)	Analysis (n/5)	Overall Quality (n/20)
Moryl et al, 2005	1	2	5	0	9
Morita et al, 2005	1	2	4	4	11
Tatematsu et al, 2011	2	2	2	2	8
Arai et al, 2013	2	2	4	2	10
Boettger and Breitbart, 2011	1	2	5	3	11
Gangon et al, 2005	1	2	4	4	11
Breitbart et al, 2002.	3	3	5	4	15

Key: 0 (very poor) 5 (excellent)