2020

Multi-disciplinary and pharmacological interventions to reduce post-operative delirium in elderly patients: A systematic review and meta-analysis

Ezinne Oyidia Igwe
University of Wollongong, ekorie@uow.edu.au

Jessica R. Nealon
University of Wollongong, jnealon@uow.edu.au

Mohammed Mohammed
University of Wollongong

Blake A. Hickey
University of Wollongong

Kuei-Ru Chou
University of Wollongong

See next page for additional authors

Publication Details Citation

Igwe, E. O., Nealon, J. R., Mohammed, M., Hickey, B. A., Chou, K., Chen, J., & Traynor, V. (2020). Multi-disciplinary and pharmacological interventions to reduce post-operative delirium in elderly patients: A systematic review and meta-analysis. Faculty of Science, Medicine and Health - Papers: Part B. Retrieved from https://ro.uow.edu.au/smhpapers1/1516

Multi-disciplinary and pharmacological interventions to reduce post-operative delirium in elderly patients: A systematic review and meta-analysis

Abstract

Study objective: An estimated 80% of older people undergoing surgery develop postoperative delirium (POD) making them a high-risk group. Research in this area is growing fast but there is no established consensus on strategies for POD prevention or management. A systematic review and meta-analysis were conducted to synthesise data on clinical interventions used to reduce POD among older people undergoing elective and emergency surgery. **Methods:** A range of database searches generated 336 papers. A total of 25 studies met the inclusion criteria and were assessed using the Joanna Briggs Institute Critical Appraisal Checklist. The studies were undertaken across the world. **Results:** This review identified a range of intervention approaches: comparisons between anaesthetic and sedatives agents, medication-specific interventions and multidisciplinary models of care. Results found more consistencies across multidisciplinary interventions than the pharmacological interventions. In pooled analyses, haloperidol (OR 0.74; 95% CI (confidence interval) 0.44, 1.26) was not statistically significantly associated with reduced POD incidence any more than a placebo. **Conclusion:** There is a need to implement multidisciplinary interventions, as well as collaboration between clinicians on pre- and postoperative care practices regarding pharmacological interventions to more effectively reduce and manage POD in older people.

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Authors

Ezinne Oyidia Igwe, Jessica R. Nealon, Mohammed Mohammed, Blake A. Hickey, Kuei-Ru Chou, Joyce Chen, and Victoria Traynor

Multi-disciplinary and Pharmacological interventions to reduce Post-operative delirium in elderly patients: A systematic review and Meta-analysis

Ezinne O Igwe (PhD)[a]*, Jessica Nealon (PhD)[b], Mohammed Mohammed (MSc)[c], Blake Hickey (MSc)[d], Kuei-Ru Chou (PhD)[e], Kee-Hsin Chen[f], Victoria Traynor (PhD)[g]

[a]Faculty of Science, Medicine and Health
University of Wollongong NSW 2522 Australia.

Illawarra Health and Medical Research Institute,
University of Wollongong NSW 2522 Australia.
ekorie@uow.edu.au

[b]Faculty of Science, Medicine and Health
University of Wollongong NSW 2522 Australia

Illawarra Health and Medical Research Institute,
University of Wollongong NSW 2522 Australia.

jnealon@uow.edu.au

[c]Faculty of Science, Medicine and Health
University of Wollongong NSW 2522 Australia
Mkm899@uowmail.edu.au

[d]School of Medicine
Faculty of Science, Medicine and Health
University of Wollongong NSW 2522 Australia
hickey@uow.edu.au

[e]College of Nursing,
Taipei Medical University, Taipei, Taiwan
kueiru@tmu.edu.tw

[f]College of Nursing, Taipei Medical University, Taiwan
Cochrane Taiwan, Taipei Medical University, Taiwan

Department of Nursing, Wan Fang Hospital, Taipei Medical University, Taiwan
Evidence-based Knowledge Translation Center, Wan Fang Hospital, Taipei
Medical University, Taiwan
keehsin@tmu.edu.tw

[g]Faculty of Science, Medicine and Health
University of Wollongong NSW 2522 Australia

Illawarra Health and Medical Research Institute,
University of Wollongong NSW 2522 Australia.
vtraynor@uow.edu.au

***Corresponding author:**

School of Medicine,
Faculty of Science Medicine and Health,
University of Wollongong NSW 2522 Australia
Tel: +61 24 239 2219

Running title: Post-operative delirium reduction in elderly patients

Disclosures: The authors have no conflict of interest to declare.

Highlights

- An estimated 80% of older people who undergo surgery develop postoperative delirium (POD).
- There is no consensus on appropriate measures for the management of POD.
- Multidisciplinary approaches show more consistency in the management of POD.
- Evidence on the use of anti-psychotics and other medications in the management of POD is inconclusive.

Abstract

Study objective: An estimated 80% of older people undergoing surgery develop postoperative delirium (POD) making them a high-risk group. Research in this area is growing fast but there is no established consensus on strategies to for POD prevention or management. A systematic review and meta-analysis were conducted to synthesise data on clinical interventions used to reduce POD among older people undergoing elective and emergency surgery.

Methods: A range of database searches generated 336 papers. A total of 25 studies met the inclusion criteria and were assessed using the Joanna Briggs Institute Critical Appraisal Checklist. The studies were undertaken across the world.

Results: This review identified a range of intervention approaches: comparisons between anaesthetic and sedatives agents, medication-specific interventions and multidisciplinary models of care. Results found more consistencies across multidisciplinary interventions than the pharmacological interventions. In pooled analyses, haloperidol (OR 0.74; 95% CI (confidence interval) 0.44, 1.26) was not statistically significantly associated with reduced POD incidence any more than a placebo.

Conclusion: There is a need to implement multidisciplinary interventions, as well as collaboration between clinicians on pre- and postoperative care practices regarding pharmacological interventions to more effectively reduce and manage POD in older people.

Keywords: Postoperative delirium; pharmacology in older people; meta-analysis; office-based anaesthesia; guidelines

1 Introduction

With 80% of older people undergoing surgery developing postoperative delirium (POD) [1], they are a high risk group [2]. Delirium is a transient condition that "develops over a short period (usually hours to days) and tends to fluctuate during the course of the day and results in disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention; changes in cognition (e.g., memory deficit, disorientation, language disturbance, perceptual disturbance) not accounted for by a pre-existing, established, or evolving dementia [3]. Its cause is determined from evidence in the history taking, physical examination, or laboratory findings that indicate the disturbance is caused by a direct physiological consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause" [3].

Delirium causes poor outcomes, including increased mortality. As the global ageing population increases there will be a concomitant increase in POD. The financial burden of POD and its associated comorbidities was estimated to be $38 - $150 billion annually in the US [4, 5]. The four main risk factors of delirium are being over 65 years and having an acute hip fracture, serious illness or pre-existing cognitive impairment [6]. POD incidence ranges from 4.0 to 53.3% in individuals undergoing hip fractures and 3.6 to 28.3% in those undergoing elective surgery [7]. The pathophysiology of delirium remains poorly understood. Its causes are multi-factorial [8, 9] with precipitating factors of anaesthetic or antipsychotic medications [8] as well as intraoperative and postoperative blood loss, length of surgery, type of surgery, anaesthesia procedure, depth of anaesthesia, pain therapy, fluid management, total fasting time, implantation of catheters, and medication use [9]. The European Society of Anaesthesiology guidelines details the gold standard for the detection of POD (CAM and Nu-

DESC) and recommendation for its prevention [7] but evidence about effective interventions to reduce POD remains contradictory.

Specifically, in a survey of anaesthetic nurses and medical anaesthetists from Australia and Scotland, 80% reported having a workplace protocol for anaesthetic plans for older people but only just over 50% had a workplace protocol to monitor POD [10]. It is imperative that there is increased more awareness of POD among older people, as timely detection and management of POD is an important step in reducing its incidence and prevalence.

The aim of this systematic literature review and meta-analysis was to synthesise data on pharmacological and non-pharmacological interventions used to reduce POD among older people undergoing elective and emergency surgery. The specific objectives were to identify medication regimens, including anaesthetics and antipsychotics, non-pharmacological interventions and multidisciplinary models of prevention and management that reduce POD incidence and prevalence in older people.

2 Methods and materials

The literature search for this systematic review was conducted based on recommendations of the PRISMA statement [11] (Figure 1).

2.1 Search strategy

Systematic literature searches of CINAHL, Medline, Web of Science and Cochrane Library were conducted to identify studies published in English up to December 2018 on interventions aimed at reducing POD among older people. A combination of search terms including "delirium prevention", "anaesthesia," "surgery", "older people," "elderly" and "geriatric" were used to search the academic databases (Appendix 1). Two assessors reviewed the title and abstracts of publications retrieved from the search to determine which publications were to be included and a third assessor was consulted to resolve disparities about whether to include a specific publication.

2.2 Selection criteria

Studies were eligible for inclusion in this review if they met the following criteria according to PICOS:

- Study population participants were aged 65 years and older undergoing a surgical procedure requiring anaesthesia;
- Description of pharmacological and non-pharmacological (including multidisciplinary approaches) interventions to reduce POD with a comparator if used;
- Primary or secondary outcome of studies was incidence/prevalence of POD;
- Studies that used the prospective quasi-experimental or randomised controlled trial study design and;

- studies published in English.

Studies were excluded from this review if they were cohort studies or duplicated reviews with clinical outcomes not POD.

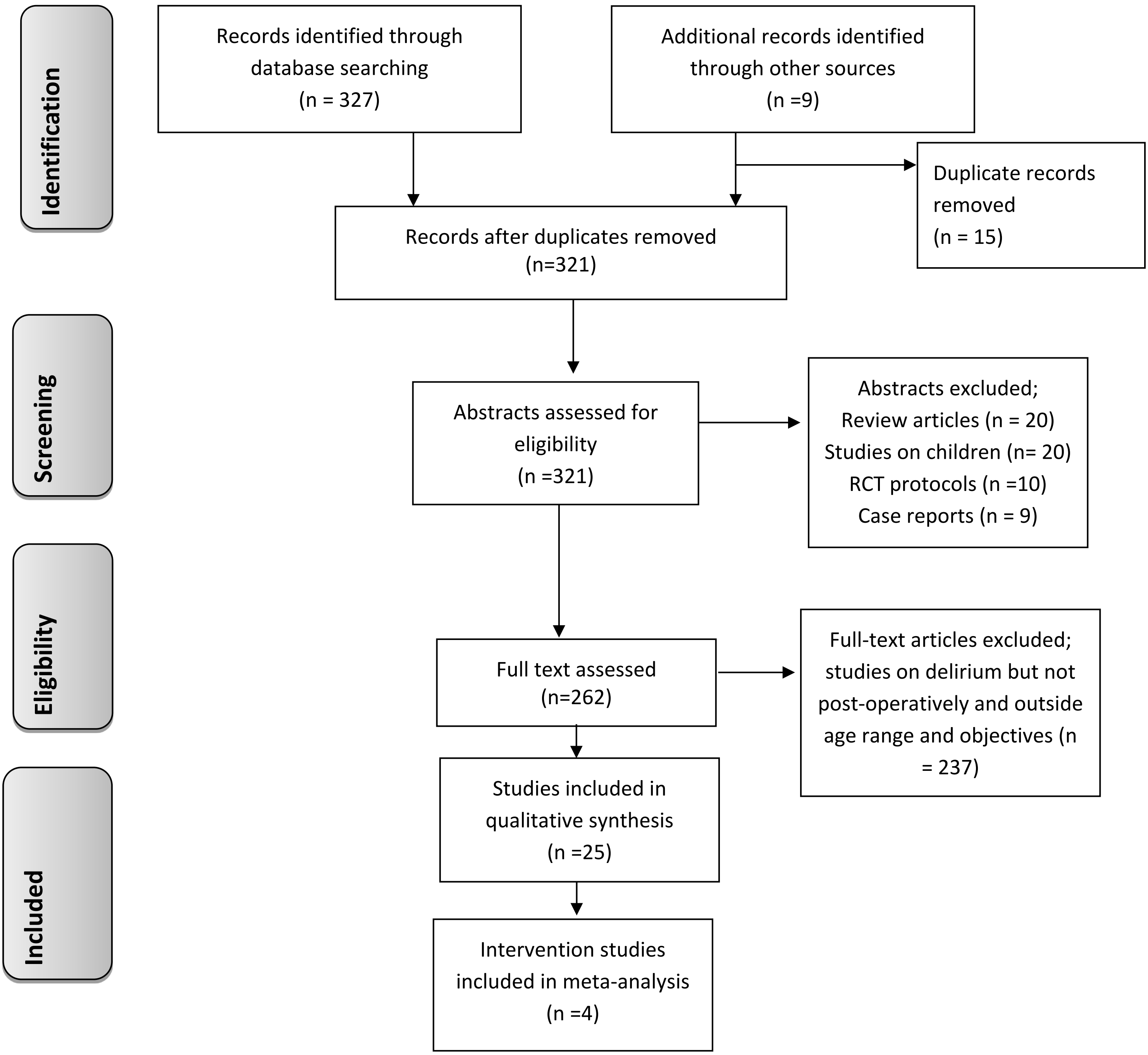
2.3 Data extraction

Data from each of the published studies included in the systematic review were extracted independently by two members of the research team and imported into a table designed specifically for this review. Data extracted consisted of study purpose/ aims; design; setting; population; intervention/comparator; data collection and analysis; results and conclusions.

2.4 Evaluation of methodological quality

Full text articles were screened for their relevance and the quality of the studies reported was evaluated using the standardised Joanna Briggs Institute (JBI) Critical Appraisal Checklist (Tables 2 and Appendix 2) [12]. Three assessors independently screened the publications, scored them based on the quality criteria and coded them as 'include' when the publication met the inclusion criteria. When ratings differed, the assessors discussed the publication to reach a consensus about its inclusion in this review. The JBI Checklist is a standardised appraisal tool used to evaluate the methodological quality of individual studies in the publications and to determine the level to which the possibility of bias was controlled for in the design, conduct and analysis of a particular study. The mean of included studies was calculated to determine the overall quality of all included studies.

Figure 1 PRISMA flowchart for study selection



2.5 Synthesis

During the synthesis stage of the systematic review, a structured approach was adopted to identify the key findings across the whole group of studies included in this review [13]. A constant comparative method was implemented to identify similar outcomes across the studies and differences in the outcomes of the interventions evaluated. This method provided the framework to present the results for the systematic literature review of interventions used to reduce POD among older people undergoing elective and emergency surgery [13].

2.6 Data analysis on a sub-set of publications included in the review

The main outcome measure for the data analysis was POD incidence. Publications on selected pharmacological interventions were merged and compared statistically in this manner. Meta-analysis was carried out on data from four of the RCTs reported in the included publications in this review, specifically studies comparing the effects of haloperidol interventions versus a control/placebo. A test for heterogeneity was conducted using the chi-square (χ^2) test and the I^2 statistic with $p<0.10$ or $I^2 >50\%$ considered significant heterogeneity. Postoperative delirium incidence (proportion) with 95% CI was calculated using the random-effects models in order to account for heterogeneity in participant populations and the nature of interventions [14]. We assessed publication bias using funnel plots (supplementary material). Meta-analysis was conducted using Cochrane Review Manager Software, RevMan Version 5.3 (The Cochrane Collaboration, Copenhagen).

3 Results

3.1 Study selection

The PRISMA flowchart for study selection (Figure 1) summarised the identification, screening and inclusion of publications for this systematic review. The initial search generated 336 publications. Following title screening and deletion of duplicates, 321 abstracts were screened, and 262 full text publications were screened further. After reading the full texts, 237 publications were excluded for the following reasons: studies of delirium in individuals not undergoing surgery and studies that did not provide POD data. Following this, 25 studies were included in the final synthesis of this systematic review. A meta-analysis was conducted on four (haloperidol interventions) out of the 13 pharmacological intervention studies as a result of low numbers in other subgroups.

3.2 Overview

A broad range of studies were published (n=25) encompassing all clinical settings and all types of intervention studies to reduce POD in older people (Table 1): (i) all types of surgery specifically, vascular, abdominal and orthopaedic surgery, and (ii) elective and emergency surgery. The calculated mean of overall quality of all included studies was 8.7 ± 1.3 (range: 5-10).

A range of standardised delirium screening tools were used in the studies to detect POD in older people (Table 1): the Confusion Assessment Method (CAM)/ CAM-ICU (n=12); the Delirium Rating Scale (DRS) (n=3); NEECHAM scale (n=1); and the Organic Brain Syndrome (OBS) scale (n=3).

Table 1 Summary of studies included in the systematic literature review

Study	Purpose/aims	Research method	Setting /Sample and Intervention	Data collection & analysis	Results, Conclusions and implications	Appraisal score (/10)
Aizawa et al, 2002 [15]	Evaluate the effects of the delirium-free protocol (DFP) in preventing POD after general surgery in older patients (≥70 yrs) patients	Prospective, randomly assigned, non-double-blind design	**Pharmacological intervention:** Surgical wards. n=42 consecutive patients who underwent resection of gastric or colorectal cancer under general anaesthesia. **Intervention:** DFP group given intramuscular injection of Diazepam at 20:00h each night and a continuous intravenous infusion of flunitrazepam and pethidine over 8h post-op **Delivery:** (Post) Intramuscular injection (0.1mg/kg).	APACHE II scores. DSM-IV. Unpaired Mann-Whitney *U*-test, Fisher's exact est.	Incidence of POD 7/20(35%) in non-DFP group and 1/20(5%) in DFP group (p=0.023)	8
Ashraf et al, 2015 [16]	Investigate whether oral premedications (diphenhydramine and diazepam) increased the risk of POD in older patients (≥70 yrs)	Single-blind RCT	**Pharmacological intervention:** Elective cardiac catheterization patients, n=93. **Intervention:** Patients randomly assigned to receive oral premedications (diphenhydramine, 5mg, and diazepam, 25 mg) vs no oral premedication before procedure. **Delivery:** Oral (pre) 5mg.	Mini-mental state examination (MMSE), CAM scores. Repeated measures ANOVA and chi-square test.	Incidence of delirium not reported in either group. Patient cooperation and ease of procedure and pain medication requirement less during and after the procedure in the pre-medicated group (p<0.05)	9
Björkelund et al, 2010 [17]	Evaluate the effects of an intervention on reducing the incidence of POD in older patients with a hip fracture (≥65 yrs)	Prospective, quasi-experimental design	**Non-pharmacological intervention:** Orthopaedic wards (n=3). n=263 older hip fracture patients: intervention (n=131) and control (n=132) **Intervention:** Multi-factorial programs (pre-hospital and peri-operative management) for patients with hip fracture including Supplemental oxygen 3–4 l/min and I.V. fluid; extra nutrition; higher vitals monitoring; Adequate pain relief; avoiding delay in transfers and polypharmacia; POD screening and Perioperative/Anaesthetic period.	OBS Scale scores, DSM IV. Fisher's exact test, Student's t-test, Mann-Whitney and Co- hen's Unweighted k scores	Incidence of delirium significantly reduced during hospitalisation from 34 to 22%. Relative risk reduction of 35% in incidence could be the result of the early interventions with intensified care	5
de Jonghe et al, 2014 [18]	Assess the effects of melatonin on the incidence of POD in older patients following hip fracture surgery (≥65 yrs)	Multicentre, double-blind RCT	**Pharmacological intervention:** Patients admitted with emergent hip fracture scheduled for surgery within 2 days. n=378 patients with hip fracture **Intervention:** patients received a tablet containing 3mg (± 5%, i.e. 2.85-3.15 mg/tablet) or placebo on 5 consecutive evenings, starting the day of admission.	MMSE, DSM-IV. Chi-square and logistic regression.	Treatment with 3 mg of melatonin did not reduce incidence of delirium. No observed between group-difference in mortality or cognitive function.	10

Study	Purpose/aims	Research method	Setting /Sample and Intervention	Data collection & analysis	Results, Conclusions and implications	Appraisal score (/10)
			Delivery: Oral (pre and post- 5 days from admission) 3mg.			
Deschodt et al, 2012 [19]	Evaluate the effects of inpatient geriatric consultation teams (IGCTs) to reduce incidence of POD and cognitive decline in older patients with POD (≥65 yrs)	Controlled trial	**Non-pharmacological intervention:** Trauma wards in a university hospital setting (n=171) patients with hip fracture (n=171): intervention (n=94) and usual care (n=77). **Intervention:** Clinical assessment: mobilisation, follow-up (anti-coagulative, non-opioid pain medications and hip x-ray), additional IGCTs consultation (post-operatively).	CAM, DI, and MMSE. Unpaired t-test Chi-square tests, The Mann–Whitney U-test	Geriatric consultation resulted in a 30% lower incidence of POD. Delirium episodes during hospitalisation were common with hip fracture, but the IGCT reduced the incidence of adverse outcomes	7
Freter et al, 2017 [20]	Investigate whether implementation of delirium friendly pre-printed orders (PPOs) by orthopaedic ward nurses reduced prevalence of POD (≥65 yrs)	Pragmatic, controlled, single-blind quality improvement study	**Non-pharmacological intervention:** Orthopaedic ward (n=283): intervention (n=144) and control (n=139). **Intervention:** Usual care PPOs (control) or delirium friendly PPOs placed in charts and attending physician signed them. Similar PPOs except for specific items e.g. urinary catheters removed on postoperative day 2 and blood work expanded to include electrolytes, urea and creatine to help identify dehydration.	MMSE and CAM. Chi-square test for categorical variables and t-test for continuous variables	Delirium-friendly PPOs implemented regular by nurses led to a significant reduction of POD (p=0.001).	7
Fukata et al, 2014 [21]	Investigate the effects of daily post-operative administration of low-dose haloperidol on reducing POD (≥75yrs)	Prospective, open-label randomised trial	**Pharmacological intervention:** Surgical wards (n=121): prophylactic intervention (n=59) and control (n=62) patients who underwent elective abdominal (under general anaesthesia) or orthopaedic surgery (under general/spinal anaesthesia). **Intervention:** Low-dose haloperidol (2.5mg/day, for first 3 days after surgery). **Delivery:** Intravenously (post) 2.5mg.	MMSE and The Neelon and Champagne (NEECHAM) Confusion Scale. Chi-square test for comparison and logistic regression for risk factors.	Preventive administration of low-dose haloperidol had no significant effect on the reduction of incidence or severity of POD.	9
Gamberini et al, 2009 [22]	Test whether short-term administration of oral rivastigmine reduces the incidence of POD in older patients (≥65 yrs)	Double-blind RCT	**Pharmacological intervention:** Cardiac surgical ward (n=113), intervention (n=56) and control (n=57). **Intervention:** three 1.5mg doses per day of rivastigmine for 6 days after surgery **Delivery:** Nasogastric tube (post) 1.5mg.	MMSE and CAM. Chi-square test, Fisher's exact test, t-test or Mann-Whitney U test.	No observed significant effect of rivastigmine on incidence or reduction of delirium.	10
Guo et al, 2016 [23]	Investigate the effects of multicomponent, non-pharmacologic interventions	Single-blind RCT		The Richmond Agitation Sedation Scale (RASS) and CAM-ICU.	After surgery the melatonin sulphate levels in the nocturnal urine was significantly higher (p<0.05) in intervention group than control group and lower in cortisol concentration	7

Study	Purpose/aims	Research method	Setting /Sample and Intervention	Data collection & analysis	Results, Conclusions and implications	Appraisal score (/10)
	(MNI) on perioperative cortisol, melatonin levels and POD on older patients (≥65 yrs)		**Non-pharmacological intervention:** Surgical ward- oral cancer surgical patients(n=160): intervention (n=81) and control (n=79). **Intervention:** multicomponent, non-pharmacological interventions based on the usual care which focused on general geriatric approaches and supportive nursing care.	Mann-Whitney U test or Student's t-test, Repeated measures ANOVA and chi-square test.	with better RASS scores (p<0.05). Significant reduction (p=0.006) in the incidence of POD in the intervention group compared to control group.	
Hakim et al, 2012 [24]	Test whether administration of risperidone to older patients who developed subsyndromal delirium (SSD) after cardiac surgery reduces the incidence of POD (≥65 yrs)	Double-blind, randomised, placebo-controlled study	**Pharmacological intervention:** Surgical ward: patient scheduled for on-pump cardiac surgery (n=101): intervention (n=51) and placebo (n=50). **Intervention:** 0.5mg of risperidone every 12 hour by mouth. **Delivery:** Oral (post) 0.5mg.	CAM-ICU, Intensive Care Delirium Checklist (ICDC) and DSM Independent samples student t-test, Mann-Whitney U test, chi-test or Fisher's exact test.	More patients in the placebo group than the intervention group experienced delirium (p = 0.031). Administration of risperidone was associated with significantly lower delirium incidence	10
Hempenius et al 2013 [25]	Evaluate the effects of a geriatric liaison intervention compared to effects of standard care on the incidence of POD in frail older patients (≥65 yrs)	Multicentre, RCT	**Non-pharmacological intervention:** Surgical ward: patients undergoing elective surgery for a solid tumour (n=297): intervention (n=148) and control (n=149). **Intervention:** multicomponent intervention focused on best supportive care and prevention of POD - preoperative geriatric consultation as well as an individual specific treatment plan targeted at delirium risk factors.	Groningen Fraility Indicator (GFI), MMSE, Delirium Observation Scale (DOS), and DSM-IV. Fisher's exact test and a 2-sample Simonov test and univariate binary logistic regression.	No observed significant difference in delirium incidence between the intervention and control group. The geriatric liaison intervention was not effective in the prevention of POD.	8
Jia et al, 2014 [26]	Determine whether Fast-Track Surgery (FTS) prevents or reduces the incidence of POD in older patients and the role of IL-6 in POD (≥70 yrs)	RCT	**Non-pharmacological intervention:** Surgical ward: patients with colorectal carcinoma admitted for open curative resection (n=240): intervention (n=120) and control (n=120) **Intervention:** Fast-track peri-operative care protocols vs traditional care protocols.	Delirium Rating Scale-Revised-98 (DRS-R-98). Wilcoxon rank-sum test, and chi-square.	Compared to traditional perioperative management, fast-track surgery significantly reduced the incidence of POD (p=0.008) at least partly attributable to the reduction in systemic inflammatory response mediated by IL-6.	7
Kalisvaart et al, 2005 [27]	Evaluate the effects of 1.5mg of haloperidol daily vs placebo on POD incidence and deterioration of POD in hip surgery patients (≥70 yrs)	Double-blind, randomised, placebo-controlled trial	**Pharmacological intervention:** Surgical and orthopaedic wards: patients admitted for acute or elective hip surgery (n=430): interventio(n=212) and control (n=218). **Intervention:** 1.5mg (0.5mg 3x/day) of haloperidol from day of admission to 3 days post-surgery. **Delivery:** (pre and post) 1.5mg/d.	MMSE, DSM-IV and CAM. Fisher's exact test, student's t-test and Mann-Whitney U test.	Low-dose haloperidol prophylactic treatment was not effective in reducing the incidence of POD and no effect on the severity or duration of POD.	10
Kaneko et al, 1999 [28]	Evaluate the effects of the use of haloperidol on reducing incidence of POD (≥65 yrs)	Randomized, comparative clinical	**Pharmacological intervention:** Surgical ward: patients scheduled for elective gastrointestinal	DSM-III-R. Student's t-test and chi-square test.	Incidence of POD was 10.5% (4 of 38 patients) in the intervention group compared to 32.5% (13 of 40 patients) in the saline treatment group.	7

Study	Purpose/aims	Research method	Setting /Sample and Intervention	Data collection & analysis	Results, Conclusions and implications	Appraisal score (/10)
			surgery received (n=78),: intervention (n=38 and control (n=40). **Intervention:** 5 mg of haloperidol intravenously postoperatively for 5 consecutive days, or normal saline with the same schedule. **Delivery:** Intravenous (post) 5mg.			
Larsen et al, 2010 [29]	Evaluate the effects of the perioperative administration of olanzapine on the prevention of POD in older patients undergoing elective joint replacement surgery (≥65 yrs)	Double-blind placebo-controlled trial	**Pharmacological intervention:** Surgical ward: patients scheduled for elective total knee- or total hip-replacement surgery (n=495): intervention (n=243) and control (n=252). **Intervention:** 5mg of oral olanzapine or placebo just before and after surgery. **Delivery:** Oral (pre and post) 5mg.	DSM-III-R, MMSE, DSR-R-98 and CAM. Student's t-test, Wilcoxon rank sum test and chi-square test.	Compared to placebo, pre-operative administration of 10mg of oral olanzapine resulted in a significantly lower incidence of POD (p<0.05), however, POD lasted longer with more severity in the intervention group.	10
Liu et al, 2016 [30]	Evaluate the effects of intravenously administered dexmedetomidine during general anaesthesia on POD in older patients with a MCI undergoing elective hip joint or knee joint or shoulder joint replacement surgery (≥65 yrs)	Double-blind RCT	**Pharmacological intervention:** Surgical ward: aMCI (n=80) and normal older patients (n=120) who underwent a total hip joint or knee joint or shoulder joint replacement surgery with general anaesthesia. **Intervention:** DEX or normal saline infusion during surgery. Four groups of aMCI DEX group (n=40), aMCI normal saline group (n=40), a control DEX group (n=60) and a control normal saline group (n=60) **Delivery:** Infusion (during surgery) 0.2-0.4µg/kg/h.	CDR, MMSE, Montreal Cognitive Assessment (MoCA) and CAM. Pearson chi-square, Fisher's exact test, ANOVA and Spearman's rank correlation test.	Positive correlation between age and POD in the aMCI normal saline group (p<0.05) but not in the control normal saline group. DEX treatment significantly reduced the incidence of POD in both control and aMCI groups compared to their respective control groups (p<0.05).	9
Lundstrom et al, 2007 [31]	Examine the effects of a postoperative multi-factorial intervention program, including comprehensive geriatric assessment, management and rehabilitation on reducing POD in patients undergoing surgery for hip fractures (≥70 yrs)	Single-blind RCT	**Non-pharmacological intervention:** Orthopaedic department: patients with hip fractures scheduled for surgery (n=199): intervention (n=102) and control (n=97). **Intervention:** Post-operative care in geriatric ward with a special intervention program which involved staff education focusing on the detection, prevention and management of POD and related complications.	MMSE, Geriatric Depression Scale (GDS-15), Organic Brain Syndrome (OBS) scale. Student's t-test, chi-square test, Fisher's exact test and multivariate linear regression.	Significantly reduced incidence of POD (p<0.05) and fewer days of POD (p<0.05) in the intervention group compared to the control group.	8
Mouzopoulos et al, 2009 [32]	Assess the effects of facia iliaca compartment block (FICB) for prevention of POD in hip surgery patients who were at intermediate or high risk for this complication (≥70 yrs)	Single-blind randomised, placebo-controlled clinical trial	**Pharmacological intervention:** Orthopaedic ward: older patients admitted for hip fracture scheduled for hip surgery (n=219): FICB prophylaxis (n=108) and placebo (n=111).	MMSE, GDS, DSM-IV and CAM. Relative risk with 95% CI.	No significant difference in delirium incidence observed in high risk patients between FICB prophylaxis and placebo. In the intermediate-risk group, FICB prophylaxis significantly (p<0.05) prevented delirium occurrence as a result. FICB could benefit in intermediate–at risk patients.	8

Study	Purpose/aims	Research method	Setting /Sample and Intervention	Data collection & analysis	Results, Conclusions and implications	Appraisal score (/10)
			Intervention: FICB administration with a 0.25mg dose of 0.3mL/kg bupivacaine pre- and postoperatively.			
Marcantonio et al, 2011 [33]	Determine whether hydrochloride reduces the prevalence and severity of POD in older patients undergoing hip fracture surgery (≥70 yrs)	Double-blind randomised pilot trial	**Pharmacological intervention:** Orthopaedic ward: patients admitted for surgical repair of hip fracture (n=16): donepezil (n=7) and placebo (n=9). **Intervention:** 5mg capsules of donepezil daily for 30 days. **Delivery:** Oral (ore and/or post) 5mg.	MMSE, Delirium Symptom Interview (DSI) and CAM. Chi-square test and Wilcoxon rank sum test and repeated measure time-independent multivariate analyses using Generalised Estimating Equations	No significant differences in the prevalence or severity of delirium between the intervention and placebo groups.	10
Nishikawa et al, 2004 [34]	Compare the effects of Propofol and sevoflurane on recovery characteristics and the incidence of POD in laparoscopic surgery (≥65 yrs)	RCT	**Pharmacological intervention:** Elective laparoscopic surgical wards (n=2). n=50 older patients: propofol n=25 and sevoflurane n=25). **Intervention:** Propofol used for anaesthesia during surgery. Oxygen, epidural analgesia, anaesthesia induction and maintenance (intra-operatively).	Anaesthesia and surgery time record, VAS, DRS and DSM-III. Mann-Whitney U-test, Student's t-test, and Fisher's exact test.	Sevoflurane less effective on reducing the occurrence of POD compared with propofol for long-duration laparoscopic surgery in older patients. Immediate emergence i.e. eye opening and extubation was significantly faster after sevoflurane (P < 0.05).	9
Pesonen et al, 2011 [35]	Study the influence of pregabalin on POD (≥75 yrs)	Randomised placebo-controlled trial	**Pharmacological intervention:** Surgical ward: patients undergoing primary elective coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) or single valve repair or replacement with CPB (n=70): pregabalin (n=35) and placebo (n=35). **Intervention:** 150mg of pregabalin surgery and 75mg of pregabalin twice daily for 5 post-operative days. **Delivery:** Orally, (pre and post) 150mg.	MMSE, RASS and CAM-ICU. Student's t-test, Fisher's exact test, Mann-Whitney U-test, chi-square test and ANOVA.	Administration of pregabalin reduced the incidence of delirium (p<0.05) compared to placebo.	9
Sieber et al, 2010 [36]	Determine whether sedation depth during spinal anaesthesia decreases the prevalence of POD (≥65 yrs)	Double- blind RCT	**Non-pharmacological intervention:** Hip fracture surgical wards (n=2). n=114 older patients: free of delirium: deep sedation (n=57) and light sedation (n=57). **Intervention:** measurement of sedation depth as well as oxygen and I.V fluid. Sedation and analgesia: propofol, midazolam and fentanyl (pre- and post-operatively).	CAM, MMSE, electroencephalogram. Fisher's exact test, Log-linear techniques, Mann-Whitney test	Use of light propofol sedation reduced the incidence of POD by 50% compared with deep sedation.	9
Stenvall et al, 2012 [37]	Investigate whether a multi-disciplinary post-operative intervention program reduces	RCT	**Non-pharmacological intervention:** Orthopaedic department at Umea University Hospital (n=1).	MMSE, OBS and DSM-IV. Student's t-test, Pearson's Chi-square test, Fisher's	Multi-disciplinary program reduced delirium (p = 0.002). Significant reduction in number of delirious days (P=0.003) and delirium on discharge (P<0.001).	8

Study	Purpose/aims	Research method	Setting /Sample and Intervention	Data collection & analysis	Results, Conclusions and implications	Appraisal score (/10)
	post-operative complications, especially POD (≥70yrs)		n=64 patients with hip fracture: intervention (n=28) and control (n=36). **Intervention:** Staff education, individualised care planning and rehabilitation, active prevention, detection and management of post-operative complications, especially POD.	exact test and Mann-Whitney U-test.		
Su et al, 2016 [38]	Investigate whether prophylactic intravenous infusion of low-dose dexmedetomidine decreases POD in older patients (≥65 yrs)	Double-blind randomised placebo-controlled trial	**Pharmacological intervention:** ICU: n=700 patients who underwent elective non-cardiac surgery under general anaesthesia, =intervention (n=350) and control (n=350). **Intervention:** dexmedetomidine hydrochloride 200µg/ 2mL. **Deliver:** Intravenous (post), 0.1µg/kg/h.	CAM-ICU, RASS and Numeric Rating Scale (NRS). Unpaired t-test, Mann-Whitney U test, chi-square test and Kaplan- Meier estimator.	Incidence of POD significantly reduced in the dexmedetomidine hydrochloride group (p<0.0001).	10
Wang et al, 2012 [39]	Evaluate the effects of low-dose intravenous haloperidol for POD prevention in critically ill patients after non-cardiac surgery (≥65 yrs)	Prospective, double- blind, RCT	**Pharmacological intervention:** ICU in non-cardiac surgery wards (n=2). n=457 patients: intervention (n=229) and placebo (n=228). **Intervention:** Haloperidol 0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hours. Analgesia and sedation (pre- and post-operatively). **Delivery:** 0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs (post).	Sedation by RASS, Delirium by CAM-ICU. Student's t-test or Mann-Whitney U test and Fisher's exact test	Administration of low dose intravenous haloperidol significantly decreased the incidence of delirium during the first 7 post-operative days. Haloperidol significantly delayed the onset of POD.	9

Table 2 : Appraisal scoring mechanism

Accepted papers	**Question numbers Key: (Y=Yes, N=No, UC=Unclear, NA= Not Applicable)**										Total JBI Score (/10)
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Aizawa et al, 2002 [15]	Y	N	N	Y	Y	Y	Y	Y	Y	Y	8
Ashraf et al, 2015 [16]	Y	UC	Y	Y	Y	Y	Y	Y	Y	Y	9
Björkelund et al, 2010 [17]	N	N	N	NA	N	Y	Y	Y	Y	Y	5
de Jonghe et al, 2014 [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Deschodt et al, 2012 [19]	N	N	Y	NA	Y	Y	Y	Y	Y	Y	7
Freter et al, 2017 [20]	Y	Y	N	Y	N	N	Y	Y	Y	Y	7
Fukata et al, 2014 [21]	Y	N	N	Y	Y	Y	Y	Y	Y	Y	8
Gamberini et al, 2009 [22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Guo et al, 2016 [23]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	8
Hakim et al, 2012, [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Hempenius et al, 2013 [25]	Y	N	N	Y	Y	Y	Y	Y	Y	Y	8
Jia et al, 2014 [26]	Y	N	N	Y	N	Y	Y	Y	Y	Y	7
Kalisvaart et al, 2005 [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Kaneko et al, 1999 [28]	Y	Y	UC	N	UC	Y	Y	Y	Y	Y	7
Larsen et al, 2010 [29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Liu et al, 2016 [30]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9
Lundstrom et al, 2007 [31]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9

Accepted papers	Question numbers Key: (Y=Yes, N=No, UC=Unclear, NA= Not Applicable)										Total JBI Score (/10)
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Marcantonio et al, 2009 [33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Mouzopoulos et al, 2009 [32]	Y	Y	UC	Y	UC	Y	Y	Y	Y	Y	8
Nishikawa et al, 2004 [34]	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	9
Pesonen et al, 2011 [35]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9
Sieber et al, 2010 [36]	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	9
Stenvall et al, 2012 [37]	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	9
Su et al, 2016 [38]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Wang et al, 2012 [39]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10

3.3 Intervention description

The publications included in this review were intervention studies undertaken with older people admitted to hospital to undergo surgical procedures. The interventions were classified as pharmacological or non-pharmacological and were started pre- or post-operatively depending on the nature of intervention. The dosage for pharmacological interventions was based on current clinical practice as specified in each individual study. For non-pharmacological interventions, the duration of intervention was based on usual hospital practice.

3.4 Results of individual studies

The intervention, comparator and results were described for this literature review (Table 1). The primary outcome of most of the studies reviewed was the incidence and prevalence of POD but for one study it was a secondary objective [35]. Pooled analysis of haloperidol interventions showed no significant effect on POD incidence (OR= 0.74, 95%CI = 0.44-1.26). At the time of this manuscript preparation, the 2014 version of the JBI checklist was used to assess methodological quality of included studies. In 2017, the JBI Appraisal checklist was updated [40].

3.4.1 Pharmacological interventions

There was a total of 16 pharmacological interventions, made up of 3 anaesthetic and sedative interventions [32, 34, 35], 13 medication-specific interventions and nine non-pharmacological, including multidisciplinary interventions. In the pharmacological category, haloperidol and dexmedetomidine were the commonly studied medications which were the medication of choice in four and two studies respectively. A meta-analysis was carried out on the haloperidol interventions (Figure 1).

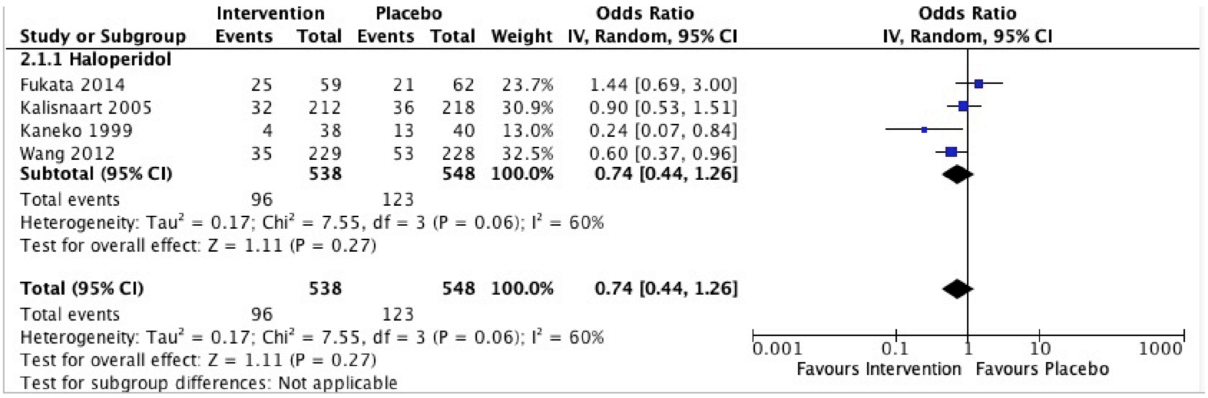
3.4.2 Medication-specific interventions

A total of 13 publications [15, 16, 18, 21, 22, 24, 27-30, 33, 38, 39] studied the effect of medication-specific interventions on POD incidence. In two of the studies [30, 38] dexmedetomidine was administered to individuals undergoing non-cardiac surgery and knee, hip and shoulder joint surgery respectively. In one study, older people undergoing cardiac surgery received a pre-medication dose of diazepam (5mg) or diphenylhydramine (25mg). In both groups no POD incidence was recorded [16]. Other medications used were ketamine, melatonin, tryptophan and haloperidol for older people undergoing a range of surgeries. In a meta-analysis on haloperidol, there was no significant effect observed (OR= 0.74, 95%CI = 0.44-1.26). No effect was observed on the reduction of POD incidence for hip-fracture [18] or orthopaedic and abdominal surgery [21].

3.4.3 Non-pharmacological interventions

There was a total of nine non-pharmacological, multidisciplinary interventions. These multidisciplinary interventions consisted of continuous monitoring of older people undergoing surgery, screening for POD, avoidance of polypharmacy, geriatric consultation and nurse-led POD prevention strategies across different surgical wards. Of the nine non-pharmacological interventions eight showed a significant reduction in POD incidence. Three studies designed non-pharmacological interventions, including multidisciplinary trials involving geriatric consultation [19, 25, 37]. Results showed a reduction in POD, apart from one of the study [25] which reported no reduction in POD between intervention and control groups. Other non-pharmacological studies with significant results were based on monitoring, adequate pain relief, screening and avoidance of polypharmacy in comparison to usual care [17], delirium-friendly pre-printed postoperative orders (assessments and continuous monitoring) [20], and systematic psychological training and guidance by a geriatrician [23].

Figure 2 Forest plot of effect of haloperidol intervention in four randomized controlled trials on the onset of POD.



4 Discussion

This systematic review and meta-analysis summarised the current evidence on the effectiveness of pharmacological and non-pharmacological interventions implemented to reduce POD. There was more consistency in the results from non-pharmacological interventions, including the role of multidisciplinary teams, compared to results from the pharmacological interventions where results were contradictory. However, there was no consensus on specific non-pharmacological approaches that are more effective in reducing the incidence of POD. There is need for more higher quality studies to ensure clinical practice can improve detection and management of POD. The inconsistencies observed in results from pharmacological interventions could be attributed to differences in methodology as well as the possibility that the interventions studied may be ineffective in reducing incidence of POD. Another possible explanation could be the different underlying comorbidities in older patients which limits generalisation within similar study populations. Research involving older individuals usually treat this study population as a homogenous group however, the presence of one or more underlying comorbidities presents a significant inter-individual variability in this study group [41].

4.1 Pharmacologic interventions

Different pharmacological interventions were trialled in the studies included in this review. Some of the medication-specific interventions include: dexmedetomidine, ketamine, melatonin, tryptophan and haloperidol.

A recurring theme across studies was pain management as pain post-surgery has been identified as a major risk factor for POD [42, 43]. Considering the age of a patient, appropriate pain control and improved multidisciplinary care practices to ensure patient comfort can significantly effect patient outcomes and POD incidence [44]. From this review, dexmedetomidine, a novel sedative-analgesic medication, was observed to reduce the incidence of POD in older patients [30, 38]. This finding supports previous evidence from a meta-analysis that in comparison to other sedatives, dexmedetomidine reduced POD incidence [45]. Although the study populations in the dexmedetomidine studies were different (one study included patients with mild cognitive impairment (MCI) and the other did not), there was agreement in the results from both studies. In the study that included patients with MCI [30], a significant correlation was observed between age and POD in older people with MCI but not in older people without MCI. Another study [35] observed that pregabalin, a medication used to treat neuropathic nerve pain, was effective in reducing POD incidence in older people. These studies showed that pain management in clinical practice is an important consideration in the prevention of POD.

The use of antipsychotics in the management of POD are too-often the 'go-to' solution in clinical practice and studies trialling haloperidol to mitigate POD symptoms are common [46, 47]; all despite clinical guidelines explaining it should be used only in extreme patient circumstances because of the severe negative side effects it causes [7, 48-50]. This review demonstrated that using haloperidol as an intervention had no significant effect on reducing POD which is supported by clinical guidelines. The review evidence presented here was sufficiently conclusive to support the cessation of its use in relation to POD in clinical practice and trial studies.

Other pharmacological interventions that have been successfully trialled include donepezil hydrochloride; used to mitigate symptoms of mild to moderate dementia evident in older people with cognitive impairment. Even though donepezil hydrochloride reduces symptoms of dementia which has overlapping features with POD [51], studies have shown that this medication has no significant effect on POD incidence [32, 52]. There is a possibility that the pathophysiology of POD and dementia are different and as a result, donepezil hydrochloride which mitigates dementia symptoms has no effect on POD. More in depth research needs to be conducted with donepezil hydrochloride in order to determine its efficacy in reducing POD incidence.

Conditions related to abnormalities in melatonin metabolism have been associated with delirium [53, 54]. One study [18] explored this hypothesis by supplementing older people with hip fracture with melatonin for five consecutive days following hospital admission but no reduction in POD incidence for older people with hip fracture was observed.

Some studies have indicated that choice of anaesthesia may impact on cognitive status and delirium in older patients. However, there is a paucity of evidence on the effects of anaesthesia on POD incidence. Two studies included in the current review compared three medications. One study [34] compared the effectiveness of propofol-based vs. sevoflurane-based anaesthesia in relation to onset of POD. From their observation, they concluded that sevoflurane was a better option than propofol for general anaesthesia with respect to POD incidence. On the other hand, another study [55] compared sevoflurane-based anaesthesia to a less common anaesthetic gas, xenon. Their aim was to investigate its feasibility and safety due to its limited use in cardiac surgery population groups. Their results showed no difference in POD incidence between the two groups. These results show that xenon- and sevoflurane-based anaesthesia is more feasible and safer than propofol-based anaesthesia in relation to POD incidence. More research is required to determine the role of anaesthetic medications on POD incidence.

One area that was lacking is the studies included in this review was taking into account the home medication of the study populations. It is therefore not possible to determine whether the use of home medications is an important factor to consider when assessing their effectiveness for reducing POD. One study on non-pharmacological intervention [17] observed that participants in both intervention and control groups treated with anticholinergic medications were more likely ($p<0.05$) to develop POD. The effects of home medications on pharmacological interventions used to reduce POD needs to be further studied.

Overall, in relation to pharmacological interventions to reduce POD incidence and prevalence in older people undergoing surgery, evidence to-date suggests that appropriate pain control/management with, either a sedative or analgesic agent, is the most effective method.

4.2 Non-pharmacologic interventions

Non-pharmacological interventions are often multidisciplinary. Results from the multidisciplinary interventions included in this review achieved significant reductions in the incidence and prevalence of POD. Education, awareness and multidisciplinary collaboration around POD prevention and management was a common non-pharmacologic intervention. [17, 19, 20, 23, 26, 31, 36, 37]. Most of these studies resulted in significant reductions in POD incidence and prevalence. Only one of the non-pharmacological intervention studies found no significant reduction in POD both in the intervention and control groups [25]. Their study included only a geriatric liaison team as the sole component of the intervention. That is perhaps a reason why their study did not achieve significant reductions in POD. Environmental factors as well as early detection and management, which comes from awareness and education of staff, is an important step in reducing POD. There is a possibility that the geriatric liaison team did not make a difference as no supplementary delirium care education was included in the geriatric liaison team intervention.

Melatonin abnormalities associated with POD onset has also been examined using non-pharmacological interventions. Guo et. al., [23] found that a multicomponent, non-pharmacologic intervention improved some postoperative disturbances including sleep and stress disorders associated with melatonin metabolism which are major risk factors for POD. Guo et. al., [56] determined that in older people who underwent total hip arthroplasty (THA) for hip fracture, older age, a history of stroke, lower albumin, higher blood glucose, higher total bilirubin, higher C-reactive protein, longer surgery duration and higher volume of red blood cell transfusions were independent risk factors for POD. It is important that preoperative care of older people includes assessment of these factors at hospital presentation to identify those at risk of developing POD and that steps are taken to manage the risk factors effectively.

The use of antipsychotics should be managed in accordance with best practice and legislation. A meta-analysis of antipsychotic medications for prevention and management of delirium in hospitalised adults observed that although there was a heterogeneity in study design and population, antipsychotic pharmacotherapy had no significant effect on the prevention or management of delirium among adult population groups during a hospital admission [57]. There was significant association between the use of antipsychotic medications and improvements on short-term mortality, severity or duration of delirium, and length of ICU and hospital stay [57].

Results from this review show that routine clinical care practices significantly reduced POD compared to pharmacological interventions. Studies on medications especially antipsychotics showed that the use of these medications did not consistently reduce POD compared to placebo. It is imperative that clinical care standards incorporate patient care practices and staff education more than new medication protocols in the prevention and management of POD. Creating greater understanding about delirium detection, prevention and management in clinical settings is the first step in reducing the incidence and prevalence of POD especially in the older population. One study explored early detection of delirium by nursing staff in order to manage its incidence before onset to decrease adverse events associated with delirium [58]. The authors observed that screening for delirium increased awareness of nursing staff, indicating the need for more emphasis on early intervention in obvious symptoms.

A limitation of this review was the variation in the tools used to diagnose POD in the studies reviewed (see results). However, CAM (CAM-ICU), which has been identified as the gold-standard for POD detection was the commonly used tool or the 4AT a newer tool demonstrating its efficacy for delirium screening [59]. This reduced the potential for this review to generalise the study outcomes. Another limitation in this meta-analysis was the high (60%) heterogeneity conducted on the haloperidol interventions. Heterogeneity might be due to the differences in the timing of the medication administration i.e. pre- and post-surgery. This emphasises the need to conduct higher quality robust studies using medication-specific interventions.

In conclusion, there were more consistencies in the non-pharmacological approaches included in this review to prevent and manage POD. This could be attributed to the heterogeneity across study populations, ineffectiveness of medication-specific interventions in reducing POD incidence as well as underlying comorbidities in patients. Pooled analysis of haloperidol, an antipsychotic, did not seem to have a significant effect on POD incidence. There is need for a general consensus on the most effective way to prevent and manage POD, especially among older people where there are higher incidence and prevalence rates. Studies included in this review did not take into account the home medication regime of participants. A few of the studies recorded the current medications on admission of the participants but these were not taken into account in data analysis or any potential clinical effects. In the future, this will be an important consideration in the planning aspect of similar studies on anticholinergic medication effects. It is also important to explore the impact of studying older people with and without preoperative cognitive impairment, dementia or mild and major neurocognitive degeneration (NCD) in relation to POD to further understand its progression. In addition, understanding the clinical practice around POD and ways to implement protocols to screen for delirium in older population groups undergoing surgery is of note in future studies. In addition, another important consideration for future research is multidisciplinary collaboration between clinicians. This could shed some light on more effective ways to reduce POD among older people and subsequently ease the financial burden associated with POD. With a growing body of evidence, internationally, about the effects of age is a significant risk factor for POD, it is imperative that evidence summaries such as this one are continuously updated.

Authors Contribution

MM, JN, BH and VT planned the study, EI, JN and MM contributed to the literature search and produced the summary tables. MM, EI, JN, BH and VT, independently and as a group, assessed included articles for methodological quality. EI and MM produced the first draft of the manuscript. All authors contributed to writing and editing of the manuscript and approved the final version of the manuscript submitted for publication.

5 References

1. Zhang, H., Y. Lu, M. Liu, Z. Zou, L. Wang, F.-Y. Xu, et al., *Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials.* Critical Care, 2013. **17**(2): p. R47.
2. Shipway, D., D. Harari, and J. Dhesi, *Peri-operative management of older people undergoing surgery.* Reviews in Clinical Gerontology, 2014. **24**(1): p. 78-92.
3. American Psychiatric Association, *Diagnostic and statistical manual of mental disorders (DSM-5®)*. 2013, Arlington, VA: American Psychiatric Publishing.
4. Inouye, S.K., T. Robinson, C. Blaum, J. Busby-Whitehead, M. Boustani, A. Chalian, et al., *Postoperative delirium in older adults: best practice statement from the American Geriatrics Society.* Journal of the American College of Surgeons, 2015. **220**(2): p. 136-148. e1.
5. Leslie, D.L., E.R. Marcantonio, Y. Zhang, L. Leo-Summers, and S.K. Inouye, *One-year health care costs associated with delirium in the elderly population.* Archives of internal medicine, 2008. **168**(1): p. 27-32.
6. Young, J., L. Murthy, M. Westby, A. Akunne, and R. O'Mahony, *Diagnosis, prevention, and management of delirium: summary of NICE guidance.* Bmj, 2010. **341**: p. c3704.
7. Aldecoa, C., G. Bettelli, F. Bilotta, R.D. Sanders, R. Audisio, A. Borozdina, et al., *European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium.* European Journal of Anaesthesiology (EJA), 2017. **34**(4): p. 192-214.
8. Lee, H.B., S.C. Mears, P.B. Rosenberg, J.M.S. Leoutsakos, A. Gottschalk, and F.E. Sieber, *Predisposing factors for postoperative delirium after hip fracture repair in individuals with and without dementia.* Journal of the American Geriatrics Society, 2011. **59**(12): p. 2306-2313.
9. Maldonado, J.R., *Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure.* International journal of geriatric psychiatry, 2018. **33**(11): p. 1428-1457.
10. Igwe, E.O., V. Traynor, S. Rodgers, A. Waite, A. MacLullich, and I. Foo, *Knowledge, opinions and clinical practice regarding postoperative delirium in older patients: A survey of nurses and anaesthetists.* Journal of Clinical Anesthesia, 2019. **57**: p. 108-109.
11. Moher, D., A. Liberati, J. Tetzlaff, D.G. Altman, and P. Group, *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS medicine, 2009. **6**(7): p. e1000097.
12. Joanna Briggs Institute, *Joanna briggs institute reviewers' manual.* Adelaide: The Joanna Briggs Institute, 2014.
13. Whittemore, R. and K. Knafl, *The integrative review: updated methodology.* Journal of advanced nursing, 2005. **52**(5): p. 546-553.
14. DerSimonian, R. and N. Laird, *Meta-analysis in clinical trials.* Controlled clinical trials, 1986. **7**(3): p. 177-188.
15. Aizawa, K.-i., T. Kanai, Y. Saikawa, T. Takabayashi, Y. Kawano, N. Miyazawa, et al., *A novel approach to the prevention of postoperative delirium in the elderly after gastrointestinal surgery.* Surgery today, 2002. **32**(4): p. 310-314.
16. Ashraf, J.M., M. Schweiger, N. Vallurupalli, S. Bellantonio, and J.R. Cook, *Effects of oral premedication on cognitive status of elderly patients undergoing cardiac catheterization.* Journal of geriatric cardiology: JGC, 2015. **12**(3): p. 257.
17. Björkelund, K.B., A. Hommel, K.G. THORNGREN, L. Gustafson, S. Larsson, and D. Lundberg, *Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study.* Acta Anaesthesiologica Scandinavica, 2010. **54**(6): p. 678-688.
18. de Jonghe, A., B.C. van Munster, J.C. Goslings, P. Kloen, C. van Rees, R. Wolvius, et al., *Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial.* Canadian Medical Association Journal, 2014. **186**(14): p. E547-E556.

19. Deschodt, M., T. Braes, J. Flamaing, E. Detroyer, P. Broos, P. Haentjens, et al., *Preventing delirium in older adults with recent hip fracture through multidisciplinary geriatric consultation.* J. Am. Geriatr. Soc., 2012. **60**(4): p. 733-739.
20. Freter, S., K. Koller, M. Dunbar, C. MacKnight, and K. Rockwood, *Translating Delirium Prevention Strategies for Elderly Adults with Hip Fracture into Routine Clinical Care: A Pragmatic Clinical Trial.* Journal of the American Geriatrics Society, 2017. **65**(3): p. 567-573.
21. Fukata, S., Y. Kawabata, K. Fujisiro, Y. Katagawa, K. Kuroiwa, H. Akiyama, et al., *Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial.* Surgery today, 2014. **44**(12): p. 2305-2313.
22. Gamberini, M., D. Bolliger, G.A.L. Buse, C.S. Burkhart, M. Grapow, A. Gagneux, et al., *Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery—a randomized controlled trial.* Crit. Care Med., 2009. **37**(5): p. 1762-1768.
23. Guo, Y., L. Sun, L. Li, P. Jia, J. Zhang, H. Jiang, et al., *Impact of multicomponent, nonpharmacologic interventions on perioperative cortisol and melatonin levels and postoperative delirium in elderly oral cancer patients.* Archives of gerontology and geriatrics, 2016. **62**: p. 112-117.
24. Hakim, S.M., A.I. Othman, and D.O. Naoum, *Early Treatment with Risperidone for Subsyndromal Delirium after On-pump Cardiac Surgery in the ElderlyA Randomized Trial.* Anesthesiology: The Journal of the American Society of Anesthesiologists, 2012. **116**(5): p. 987-997.
25. Hempenius, L., J.P. Slaets, D. van Asselt, G.H. de Bock, T. Wiggers, and B.L. van Leeuwen, *Outcomes of a geriatric liaison intervention to prevent the development of postoperative delirium in frail elderly cancer patients: report on a multicentre, randomized, controlled trial.* PloS one, 2013. **8**(6): p. e64834.
26. Jia, Y., G. Jin, S. Guo, B. Gu, Z. Jin, X. Gao, et al., *Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma.* Langenbeck's archives of surgery, 2014. **399**(1): p. 77-84.
27. Kalisvaart, K.J., J.F. De Jonghe, M.J. Bogaards, R. Vreeswijk, T.C. Egberts, B.J. Burger, et al., *Haloperidol Prophylaxis for Elderly Hip-Surgery Patients at Risk for Delirium: A Randomized Placebo-Controlled Study.* J. Am. Geriatr. Soc., 2005. **53**(10): p. 1658-1666.
28. Kaneko, T., J. Cai, T. Ishikura, M. Kobayashi, T. Naka, and N. Kaibara, *Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery.* Yonago Acta Med., 1999. **42**(3): p. 179-184.
29. Larsen, K.A., S.E. Kelly, T.A. Stern, R.H. Bode, L.L. Price, D.J. Hunter, et al., *Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial.* Psychosomatics, 2010. **51**(5): p. 409-418.
30. Liu, Y., L. Ma, M. Gao, W. Guo, and Y. Ma, *Dexmedetomidine reduces postoperative delirium after joint replacement in elderly patients with mild cognitive impairment.* Aging Clin. Exp. Res., 2016. **28**(4): p. 729-736.
31. Lundström, M., B. Olofsson, M. Stenvall, S. Karlsson, L. Nyberg, U. Englund, et al., *Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study.* Aging clinical and experimental research, 2007. **19**(3): p. 178-186.
32. Mouzopoulos, G., G. Vasiliadis, N. Lasanianos, G. Nikolaras, E. Morakis, and M. Kaminaris, *Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study.* Journal of orthopaedics and traumatology, 2009. **10**(3): p. 127-133.
33. Marcantonio, E.R., K. Palihnich, P. Appleton, and R.B. Davis, *Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture.* J. Am. Geriatr. Soc., 2011. **59**(s2).
34. Nishikawa, K., M. Nakayama, K. Omote, and A. Namiki, *Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients:*

propofol-based vs. sevoflurane-based anesthesia. Acta Anaesthesiol. Scand., 2004. **48**(2): p. 162-168.

35. Pesonen, A., R. Suojaranta-Ylinen, E. Hammaren, V. Kontinen, P. Raivio, P. Tarkkila, et al., *Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial.* British journal of anaesthesia, 2011. **106**(6): p. 873-881.
36. Sieber, F.E., K.J. Zakriya, A. Gottschalk, M.-R. Blute, H.B. Lee, P.B. Rosenberg, et al. *Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair*. in *Mayo Clin. Proc.* 2010. Elsevier.
37. Stenvall, M., M. Berggren, M. Lundström, Y. Gustafson, and B. Olofsson, *A multidisciplinary intervention program improved the outcome after hip fracture for people with dementia—subgroup analyses of a randomized controlled trial.* Arch. Gerontol. Geriatr., 2012. **54**(3): p. e284-e289.
38. Su, X., Z.-T. Meng, X.-H. Wu, F. Cui, H.-L. Li, D.-X. Wang, et al., *Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial.* The Lancet, 2016. **388**(10054): p. 1893-1902.
39. Wang, W., H.-L. Li, D.-X. Wang, X. Zhu, S.-L. Li, G.-Q. Yao, et al., *Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial.* Critical care medicine, 2012. **40**(3): p. 731-739.
40. Tufanaru C, Munn Z, Aromataris E, Campbell J, and H. L., *Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/.* 2017.
41. von Humboldt, S., I. Leal, and F. Pimenta, *What predicts older adults' adjustment to aging in later life? The impact of sense of coherence, subjective well-being, and sociodemographic, lifestyle, and health-related factors.* Educational Gerontology, 2014. **40**(9): p. 641-654.
42. Vaurio, L.E., L.P. Sands, Y. Wang, E.A. Mullen, and J.M. Leung, *Postoperative delirium: the importance of pain and pain management.* Anesthesia & Analgesia, 2006. **102**(4): p. 1267-1273.
43. Lynch, E.P., M.A. Lazor, J.E. Gellis, J. Orav, L. Goldman, and E.R. Marcantonio, *The impact of postoperative pain on the development of postoperative delirium.* Anesthesia & Analgesia, 1998. **86**(4): p. 781-785.
44. Smith, T.O., A. Cooper, G. Peryer, R. Griffiths, C. Fox, and J. Cross, *Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis.* International journal of geriatric psychiatry, 2017. **32**(4): p. 386-396.
45. Li, B., H. Wang, H. Wu, and C. Gao, *Neurocognitive dysfunction risk alleviation with the use of dexmedetomidine in perioperative conditions or as ICU sedation: a meta-analysis.* Medicine, 2015. **94**(14).
46. Schrijver, E.J., K. de Graaf, O.J. De Vries, A.B. Maier, and P.W. Nanayakkara, *Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: a systematic review of current evidence.* European journal of internal medicine, 2016. **27**: p. 14-23.
47. Hirota, T. and T. Kishi, *Prophylactic antipsychotic use for postoperative delirium: a systematic review and meta-analysis.* The Journal of clinical psychiatry, 2013. **74**(12): p. e1136-44.
48. Mohanty, S., R.A. Rosenthal, M.M. Russell, M.D. Neuman, C.Y. Ko, and N.F. Esnaola, *Optimal perioperative management of the geriatric patient: a best practices guideline from the American College of Surgeons NSQIP and the American Geriatrics Society.* Journal of the American College of Surgeons, 2016. **222**(5): p. 930-947.
49. American Geriatrics Society, *American Geriatrics Society Abstracted Clinical Practice Guideline for Postoperative Delirium in Older Adults.* Journal of the American Geriatrics Society, 2015. **63**(1): p. 142-150.

50. AHMAC, *Clinical practice guidelines for the management of delirium in older people*, Clinical Epidemiology and Health Service Evaluation Unit, Editor. 2006, Victorian Government Department of Human Services,: Melbourne.
51. Meagher, D.J., M. Leonard, S. Donnelly, M. Conroy, J. Saunders, and P.T. Trzepacz, *A comparison of neuropsychiatric and cognitive profiles in delirium, dementia, comorbid delirium-dementia and cognitively intact controls.* Journal of Neurology, Neurosurgery & Psychiatry, 2010. **81**(8): p. 876-881.
52. Sampson, E.L., P.R. Raven, P.N. Ndhlovu, A. Vallance, N. Garlick, J. Watts, et al., *A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement.* International journal of geriatric psychiatry, 2007. **22**(4): p. 343-349.
53. Shilo, L., Y. Dagan, Y. Smorjik, U. Weinberg, S. Dolev, B. Komptel, et al., *Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern.* The American journal of the medical sciences, 1999. **317**(5): p. 278-281.
54. Haimov, I., *Melatonin rhythm abnormalities and sleep disorders in the elderly.* CNS spectrums, 2001. **6**(6): p. 502-506.
55. Stoppe, C., A. Fahlenkamp, S. Rex, N. Veeck, S. Gozdowsky, G. Schälte, et al., *Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study.* British journal of anaesthesia, 2013. **111**(3): p. 406-416.
56. Guo, Y., P. Jia, J. Zhang, X. Wang, H. Jiang, and W. Jiang, *Prevalence and risk factors of postoperative delirium in elderly hip fracture patients.* Journal of International Medical Research, 2016. **44**(2): p. 317-327.
57. Neufeld, K.J., J. Yue, T.N. Robinson, S.K. Inouye, and D.M. Needham, *Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis.* Journal of the American Geriatrics Society, 2016. **64**(4): p. 705-714.
58. Malik, A., T. Harlan, and J. Cobb, *Stop. Think. Delirium! A quality improvement initiative to explore utilising a validated cognitive assessment tool in the acute inpatient medical setting to detect delirium and prompt early intervention.* Journal of clinical nursing, 2016. **25**(21-22): p. 3400-3408.
59. Tieges, Z., A.M. MacLullich, A. Anand, C. Brookes, M. Cassarino, M. O'Connor, et al., *Diagnostic Accuracy of the 4AT for delirium detection: systematic review and meta-analysis.* medRxiv, 2020.

Appendix 1 Example Search strategy (search terms used)

Example search strategy **Source: Medline**
TITLE-ABS-KEY (Delirium AND anaesthe* AND surg* AND (elder* OR aged OR older OR geriatric)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp") OR LIMIT-TO (DOCTYPE , "ip")) AND (LIMIT-TO (LANGUAGE , "English"))
The * indicates a truncation, to ensure all variations of the search terms were included.

Appendix 2 : Joanna Briggs Institute (JBI) Appraisal Questions

Question numbers	Joanna Briggs Institute Appraisal Question
1.	Was the assignment to treatment groups truly random?
2.	Were participants blinded to treatment allocation?
3.	Was allocation to treatment groups concealed from the allocator?
4.	Were the outcomes of people who withdrew described and included in the analysis?
5.	Were those assessing the outcomes blind to the treatment allocation?
6.	Were the control and treatment groups comparable at entry?
7.	Were groups treated identically other than for the named intervention?
8.	Were outcomes measured in the same way for all groups?
9.	Were outcomes measured in a reliable way?
10.	Was appropriate statistical analysis used?