

The effectiveness and harms of pharmacological interventions for the treatment of delirium in adults admitted into the intensive care unit after cardiac surgery: a systematic review

A thesis submitted by
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ABBREVIATIONS

ABCDE	Awakening, Breathing, Coordination, Delirium monitoring/management and Early exercise/mobility
ABG	Arterial Blood Gas
APA	American Psychiatric Association
APACHE	Acute Physiology and Chronic Health Evaluation
AVR	Aortic Valve Repair or Replacement
BD	“Bis in die”, twice daily
BMI	Body Mass Index
BP	Blood Pressure
CABG	Cardiopulmonary Bypass Graft
CAM-ICU	Confusion Agitation Method – Intensive Care Unit
CNS	Central Nervous System
CO	Cardiac Output
CONSORT	Consolidated Standards of Reporting Trials
CPB	Cardiopulmonary Bypass
CTD	Cognitive Test for Delirium
d	Dose
DDS	Delirium Detection Score
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBHC	Evidence-Based Healthcare
EBM	Evidence-Based Medicine
ECG	Electrocardiogram
EF	Ejection Fraction
FAME	Feasible, Appropriate, Meaningful, Effective

FDA	Food and Drug Administration
GABA	Gamma Aminobutyric Acid
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Heart Rate
hr	Hour
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
IM	Intramuscularly
IV	Intravenously
JBI	Joanna Briggs Institute
kg	Kilograms
min	Minute
mg	Milligram
MVR	Mitral Valve Repair or Replacement
NAH	Neuronal Aging Hypothesis
NDH	Network Dysconnectivity Hypothesis
NEH	Neuroendocrine Hypothesis
NICE	National Institute of Care and Excellence
NIH	Neuroinflammatory Hypothesis
NTH	Neurotransmitter Hypothesis
Nu-DESC	Nursing Delirium Screening Scale
OSH	Oxidative Stress Hypothesis
PaCO ₂	Partial Pressure of Carbon Dioxide
PAD	Pain, Agitation, Delirium
PaO ₂	Partial Pressure of Oxygen

PICO	Population, Intervention, Comparator, Outcome
PNS	Peripheral Nervous System
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RASS	Richmond Agitation Sedation Score
RCT	Randomised Controlled Trial
RR	Respiration Rate
SoF	Summary of Findings
SOFA	Sequential Organ Failure Assessment
SpO ₂	Saturated Peripheral Oxygen Level
TAVI	Transcatheter Aortic Valve Implantation
TISS 28	Therapeutic Intervention Scoring System

ABSTRACT

Background

Patients who undergo cardiac surgery are at high risk of delirium (incidence: 50-90%), increasing the risk of death and adversely affecting recovery. Clinical interventional trials have been conducted to prevent and treat postoperative delirium pharmacologically including antipsychotics and sedatives. These trials have provided some evidence about efficacy and influenced clinical decision making. However, much reporting is incomplete and provides biased assessments of efficacy; benefits are emphasised while harms are inadequately reported. The purpose of this study was to undertake a systematic review using the Joanna Briggs Institute (JBI) methodology that aimed at identifying and synthesising the best available evidence about the effectiveness and harms of pharmacological interventions in the treatment of delirium in adult intensive care patients after cardiac surgery.

Inclusion Criteria

Types of participants

Participants were ≥ 16 years, any gender or ethnicity, who were treated postoperatively in a cardiothoracic intensive care unit (ICU) following cardiac surgery and identified as having delirium.

Types of interventions

Any pharmacological intervention for the treatment of delirium was included, regardless of drug classification, dosage or frequency of administration.

Types of comparators

Studies that compared any pharmacological interventions for the treatment of delirium in patients who were admitted in the ICU after cardiac surgery. No limitations were placed on drug classification, dosage of the medications or frequency of administration.

Types of outcomes

This systematic review examined eleven primary and five secondary outcomes of interest. The primary outcomes of interest included: mortality, duration and severity of delirium, use of physical restraints, quality of life, family members satisfaction with delirium management, duration/severity of the aggressive episode, associated falls, severity of accidental self-harm, pharmacological harms, and harms related to over-sedation.

Types of studies

Randomised controlled trials (RCTs) were considered first and in their absence, non-RCTs and quasi-experimental would have been considered followed by analytical observational studies.

Search Strategy

A comprehensive search was conducted across seven databases, three clinical trial registers and a database for dissertations and theses as well as a hand search for published primary studies.

Methodological quality

Two reviewers assessed the methodological quality of the included studies using standardised critical appraisal instruments from JBI and McMaster University.

Data extraction

Quantitative data were extracted using the standardised JBI data extraction tool. A meta-analysis was not performed as there was too much clinical and methodological heterogeneity in the included studies. Results have been presented in a narrative form. Standard GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) evidence assessment of outcomes has been reported.

Results

Three RCTs investigating morphine vs haloperidol (n=53), ondansetron vs haloperidol (n=72) and dexmedetomidine vs midazolam (n=80) were included. Overall the methodological quality of these studies was found to be low. There is currently insufficient evidence to confirm or refute the effectiveness of morphine compared with haloperidol, ondansetron compared with haloperidol or dexmedetomidine compared with midazolam for reducing the duration or severity of hyperactive delirium in the postoperative cardiac surgical patient treated in the ICU. Additionally, this review found reporting of harms to be inadequate for all three studies and did not meet the required standards for harms reporting.

Conclusions

This review was unable to draw any valid conclusions regarding the effectiveness of the included pharmacological interventions in treating delirium after cardiac surgery. This is due to the low number of studies, the poor methodological quality in conducting and reporting and the heterogeneity between the studies.

Implications for practice

There is insufficient evidence to support the use of morphine, ondansetron or dexmedetomidine as effective pharmacological agents in treating delirium. It is imperative that clinicians remain vigilant to the known indications, contraindications and harms of the pharmacological agents that are being administered and to understand the implications of such drugs on cardiac performance in the initial postoperative recovery phase after cardiac surgery

Keywords

cardiac surgery; confused state; delirium; ICU; treatment; pharmacology

DECLARATION OF ORIGINALITY OF WORK

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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CHAPTER 1: INTRODUCTION

The focus of this thesis is the presentation of a systematic review following the Joanna Briggs Institute (JBI) methodology for reviewing evidence on the effectiveness of an intervention. The review question sought to identify and synthesise the best available evidence on the effectiveness and harms of pharmacological interventions for the treatment of hyperactive delirium following cardiac surgery in patients treated in the intensive care unit (ICU). The aim was to explore the effect on the following key outcomes; mortality, duration and severity of delirium, the use of physical restraints, quality of life, family members satisfaction with delirium management, duration/severity of the aggressive episode, associated falls, severity of accidental self-harm, pharmacological harms, harms related to over-sedation, ICU length of stay, hospital length of stay (after the ICU stay), total hospital length of stay, need for additional intervention medication and need for rescue medication.

1.1 Thesis structure

This thesis is organised into the following five chapters:

Chapter 1: Introduction:

In the first chapter a background to the topic of interest is provided - delirium following cardiac surgery in adults admitted into the ICU. The chapter will define delirium and explain the various subtypes of delirium. The incidence rates and associated risk factors will also be discussed before outlining the pathophysiology behind the manifestation of delirium and the recommended strategies for identifying and screening. This will then be followed with a discussion on current management and treatment strategies. Finally, an overview of the current research is also provided, along with a rationale for undertaking a systematic review on this topic.

Chapter 2: Methodology:

In chapter two, the methodological principles upon which the systematic review of international literature is based are addressed. This includes a description of the development and origins of evidence-based healthcare (EBHC), evidence synthesis and the systematic review.

Chapter 3: Systematic review methods:

In the third chapter the methodological process undertaken in the systematic review underpinning this thesis is described. Outlined in this chapter are the review objective/question, inclusion criteria including types of, participants, interventions, comparators, the primary and secondary outcomes and types of studies. The search and selection process are detailed alongside the appraisal process for methodological quality, the process utilised for data extraction and the method of data synthesis.

Chapter 4: Results:

The search results and the methodological quality and characteristics of the included studies are described in Chapter four. The findings of the review are also presented in this chapter.

Chapter 5: Discussion, conclusions and recommendations for practice and research:

In the final chapter the main findings generated from the systematic review, the limitations of the review and the implications for practice and research are discussed.

1.2 Overview of chapter 1

The remaining part of chapter one of this thesis is broken down into the following sections: an overview of delirium with reference to definition (section 1.3), delirium subtypes (section 1.4), national and international incidence rates (section 1.5), the associated risk factors for delirium (section 1.6), pathophysiology (section 1.7), recognition and screening (section 1.8), management and treatment with reference to non-pharmacological and pharmacological management (section 1.9), overview of current literature (section 1.10) and relationship between existing literature and rationale for conducting a systematic review on this topic (section 1.11).

1.3 Contextual overview of delirium

Delirium after cardiac surgery is a common phenomenon that may have unwanted short and long-term implications.¹⁻⁴ According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) V, delirium is defined as an acute alteration in cognition which is characterised by fluctuating mental alertness, confusion and behavioural disturbances.^{4, 5}

1.4 Delirium subtypes

Delirium is classified into three motoric subtypes; hyperactive (characterized by agitation, increased psychomotor activity, hallucinations and restlessness), hypoactive (characterized by reduced level of consciousness, withdrawal and inattention) and mixed (characterised by fluctuations between hyper and hypoactive subtypes) which affect sleep, psychomotor activities and emotions to differing degrees.⁶⁻⁹ Due to the restless and agitated nature of the symptoms, hyperactive delirium is easier to identify yet, it is associated with an increased risk of harm and injury to self and others.³ However, hypoactive delirium has been shown to be associated with worse outcomes compared to hyperactive and mixed delirium largely as a result of under-recognition.^{7, 8} Although reversible, delirium is a precursor to poor patient outcome following the delirium episode and this often initiates a cascade of events.^{2, 10, 11} For the patient, cognitive impairment following the delirium episode is known to affect attention and reasoning, memory and processing speed that can manifest as relatively minor to severe cognitive impairment.¹² Prolonged delirium can result in worse outcomes for up to one year following the episode; 35% of patients experiencing it die within six months of hospital discharge.¹²⁻¹⁶ The impact on the individuals' long-term health, their families, health services and the wider community is of significant public health importance.¹⁷ For the healthcare system, increased costs are incurred with prolonged length of stay, requiring additional staffing, medication, safety equipment and rehabilitation.^{2, 9, 12, 13, 18, 19} Internationally, the annual cost has been estimated at 1200€ (1909.32AUD) per diagnosed delirium patient while the cost to the Australian healthcare system has been found to be two and a half times greater than for non-delirious patients.^{2, 20}

1.5 Incidence

Delirium occurs at any age and in any setting. Patients admitted for treatment in ICU are at greatest risk.²¹ In Australia, the incidence of delirium in ICU has been reported at 37% (using unstandardised assessment methods) and 21% (using standardised assessment methods).²² In a multicentre Australian and New Zealand study, the incidence was determined to be 45% (standardised assessment) and international studies report delirium to affect 3-90% of hospitalised patients.²²⁻²⁴ The discrepancy and variation in incidence is dependent upon the methodology used to screen and assess for delirium, the characteristics of the patients (e.g. age, severity of illness) and the competence of those identifying and screening for delirium.

1.6 Associated risk factors

The risk factors associated with delirium are classified according to whether they predispose or precipitate delirium.²⁴ In cardiac surgical patients, delirium is associated with specific preoperative, intraoperative and postoperative factors.^{11, 25} There is strong evidence that preoperative predisposing risk factors may include advanced age, hypertension, decreased ejection fraction, atrial fibrillation, pulmonary hypertension, diabetes,

body mass index (BMI), impaired renal perfusion, vascular disease, cerebrovascular disease, pre-existing cognitive impairment, preoperative cognitive impairment, emergency surgery, drug and alcohol use.^{11, 17, 24, 26} Intraoperatively, open heart surgery is typically performed either with (on-pump) or without (off-pump) the use of cardiopulmonary bypass (CPB).^{11, 27-29} Incorporating CPB (on-pump) allows cardiac surgery to be performed with a bloodless field.^{27,28} Cardiopulmonary bypass involves the insertion of an extracorporeal circuit that provides circulatory and respiratory function to facilitate surgery on the heart and coronary vessels.^{27,28} Utilising CPB may be accompanied with significant hypothermia, hypoxia or hypoxemia, that is usually associated with a systemic inflammatory response and haemodynamic instability.¹¹ This is potentially due to the induced hypothermic state required for use of CPB, thus leading to patients requiring extended anaesthetic time and blood transfusions.¹¹ Studies have revealed a strong association between delirium and on-pump cardiac surgeries compared with off-pump surgeries.^{27, 29} The postoperative risk factors that may precipitate delirium include prolonged mechanical ventilation associated with continuous infusions of sedative medications, opioids for pain management, atrial fibrillation, hypotension, sleep disruption, cardiogenic shock and sepsis.¹¹ These predisposing and precipitating risk factors may be further exaggerated by the environmental impact of intensive care due to sleep deprivation, windowless rooms, noise, light disturbances and multiple occupancy rooms.³⁰ These factors have been found to disrupt patient sleep-wake cycles (circadian rhythms) placing them at greater risk of delirium.^{31, 32}

1.7 Pathophysiology

While the exact neurophysiological mechanism and causation of delirium remains unclear, there are published studies that have provided some explanation of the underlying mechanism.³³⁻³⁵ In 1998, an exploration of the pathophysiology of delirium was published by van der Mast,³⁵ providing an explanation for the underlying mechanism of delirium as being underpinned by the neurotransmitter hypothesis and the inflammatory hypothesis.³⁵ The potential cerebral dysfunction was proposed to be a result of dysregulation in cholinergic, monaminergic, cerebral γ -aminobutyric acid, glutamate and histamine neurotransmitters.³⁵ Gunther, 2008³³ developed this area further by exploring neurotransmitter dysfunction using neuroimaging, suggesting that delirious patients experienced a 42% reduction in cerebral blood flow in the subcortical and occipital regions that leads to widespread brain dysfunction.³³

A more recent explanation of the underlying mechanism of delirium was published by Maldonado in 2013.³⁴ Maldonado explored several hypotheses; the neuroinflammatory hypothesis (NIH), the neuronal aging hypothesis (NAH), the oxidative stress hypothesis (OSH), the neurotransmitter hypothesis (NTH), the neuroendocrine hypothesis (NEH), the diurnal dysregulation or melatonin dysregulation hypothesis, and finally, the network dysconnectivity hypothesis (NDH).³⁴

The NIH proposes an acute over-stimulation of inflammatory markers as a result of surgery, infection or trauma that leads to delirium symptoms.³⁴ It has been suggested that surgical procedures involving extensive tissue damage, use of anesthetic agents, blood loss requiring blood transfusions, the use of extracorporeal circulation (bypass), hypoxia, ischemia and re-perfusion may trigger inflammatory markers activating the inflammatory cascade that overwhelms the system leading to delirium.³⁴ The NAH suggests that aging leads to cerebral changes in stress-regulating neurotransmitters, reduced blood flow and vascular density and a loss of neuron and intracellular signal transduction leading to the elderly becoming increasingly vulnerable to stress and illness.³⁴ The OSH suggests that hypoperfusion induces chronic oxidative stress as a result of tissue damage, hypoxia, severe illness and infection that overwhelms oxygen and glucose availability with metabolic demand, which may lead to cerebral dysfunction.³⁴ The NTH proposes that delirium occurs as a result of substances (e.g. medications, toxins) that alter neurotransmitter function and availability, leading to imbalances in neurotransmitter function,³⁴ while the NEH proposes that delirium occurs as a result of acute stress that is mediated by abnormally high glucocorticoid steroid levels.³⁴ Glucocorticoid steroid hormones impair cerebral neurons resulting in the reduced ability of neurons to survive after various metabolic insults.³⁴ The diurnal dysregulation or melatonin dysregulation hypothesis suggests that disruptions to the 24-hour circadian cycle may lead to disturbances in sleep patterns leading to melatonin imbalances and sleep deprivation as a result of circadian rhythm disruption.³⁴ Current evidence suggests that the acute and chronic impact of sleep deprivation is associated with altered endocrine and metabolic functions, cortisol release contributing to glucocorticoid steroid hormone imbalance, glucose tolerance, insulin resistance and inflammatory processes.^{32, 34} Finally, the NDH proposes that various factors, such as toxins, disease, inflammation, aging or pharmacologic agents act on specific brain neurochemical systems (cholinergic and gamma-aminobutyric acid (GABA)) that determine the phenotype, severity and duration of the delirium episode.³⁴

In summary, it has been strongly suggested that the pathophysiological mechanism of delirium involves imbalances in several neurotransmitter pathways that lead to the development of delirium.³³⁻³⁵ Imbalances occur in the release, synthesis and degradation of GABA, glutamate, acetylcholine, norepinephrine, dopamine and serotonin leading to neurological dysfunction.^{12, 33, 36, 37} Some studies have proposed that these pathways are further influenced by metabolic disturbances which often occur during critical illness such as sepsis, inflammation, ischaemia and glucose dysfunction. Delirium often emerges when multiple predisposing and precipitating risk factors, iatrogenic or environmental factors and metabolic disturbances converge.³³⁻³⁵

1.8 Recognition and screening

Delirium after cardiac surgery is a known complication that is associated with increased morbidity and mortality.^{13,50} Early recognition, increased screening and early intervention have been shown to improve patient outcomes.^{38,39} The gold standard for delirium diagnosis is an interview conducted by a trained clinician (psychiatrist) using the DSM-IV criteria.³⁷⁻⁴⁰ However, the feasibility of this approach in the clinical setting makes it impractical.³⁸ Arguably, critical care nurses are ideally placed to recognise and screen for delirium early, particularly in this patient cohort.³⁸⁻⁴⁰ A number of delirium assessment tools have been developed to assist nurses in screening and assessment.⁴¹ The Society of Critical Care Medicine Pain, Agitation and Delirium (PAD) guideline advocates for frequent monitoring to occur at least once per shift (every 8 – 12 hours) using a valid assessment tool.^{38, 39, 42-44} Five assessment tools have been reviewed by The Society of Critical Care Medicine; the Confusion Assessment Method for ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Cognitive Test for Delirium (CTD), Delirium Detection Score (DDS) and the Nursing Delirium Screening Scale (Nu-DESC).⁴³ The CAM-ICU and ICDSC are both used for identifying delirium in both mechanically ventilated and self-ventilating patients and have been validated.⁴³ Studies conducted to compare assessment tools have revealed that the CAM-ICU may be highly sensitive while the ICDSC may have greater specificity.^{12, 18, 45, 46} However, more recent studies suggest that the two assessment tools perform differently in different populations and settings and that specificity is sometimes better for the CAM-ICU than the ICDSC.^{12, 47} The consensus among experts is that both instruments are excellent screening tools and either will provide better assessment than other instruments or an unstructured clinical assessment.^{12, 47}

1.9 Management and treatment

Due to the complex and multifactorial nature of delirium, treatment and management is challenging.^{1, 40, 48} The duration and severity of deliria has short and long-term implications.^{13, 25, 49} There is strong evidence indicating that prolonged delirium is associated with elevated Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II and Therapeutic Intervention Scoring System (TISS) 28 scores, indicating a progression of organ insufficiency, and increased risk of morbidity and mortality.^{13, 50} Unresolved delirium increases the risk of experiencing anaemia, falls, pressure injuries, renal failure, wound infections, strokes, transient ischemic attacks and pneumonia.^{25, 49} Management of delirium primarily involves identifying and correcting any underlying cause(s) and the aim is to reduce the severity and duration of the delirium episode.^{12, 51} Management strategies are categorised into either non-pharmacological or pharmacological interventions. Non-pharmacological strategies are focused towards prevention rather than treatment while pharmacological strategies target prevention and/or treatment.

Non-pharmacological interventions

Non-pharmacological intervention refers to any non-drug intervention.⁴⁰ Often initiated by the bedside nurse, non-pharmacological interventions are designed to reduce environmental risk factors and are therefore preventative rather than treatment strategies.⁴⁰ A number of non-pharmacological interventions have been attempted including sleep promotion, noise and light management, music therapy, patient re-orientation and early mobilisation.^{40, 43}

Studies conducted to examine the efficacy of non-pharmacological strategies tend to be performed as multi-component complex interventions such as care bundles or clusters rather than in isolation and have shown promising results.⁴⁰ Inouye et al, 1999 conducted a controlled clinical trial on non-pharmacological multi-component interventions, reporting a 40% decrease in the incidence of delirium in the target group.⁵² Similar results have been reported in additional studies where non-pharmacological interventions have been studied as care bundles and implemented using a multidisciplinary team approach.^{38, 40, 43, 53, 54} Non-pharmacological intervention studies conducted to examine the efficacy of individual interventions are limited. A review exploring the potential relationship between sleep deprivation and delirium revealed the mechanism was largely unknown and recommended further studies to be conducted with ICU patients rather than non-ICU patients.³⁷ More recently, a systematic review was conducted exploring the effectiveness of both pharmacological and non-pharmacological interventions on the treatment of delirium in the elderly and revealed little evidence of the effectiveness of either for managing the deliria episode.⁵⁵

Non-pharmacological care bundles with a multidisciplinary team approach is a widely recommended approach outlined in clinical guidelines for the pre-eminent professionals responsible for managing the condition.^{18, 43, 56} Environmental interventions and cognitive-emotional support provided by nurses, general medical and psychiatric clinicians are suggested together with supportive measures that minimise the exacerbation of the delirium through re-orientation, reassurance and education measures.¹⁸ A multidisciplinary approach in which care is tailored to meet the patient's needs is advocated in the National Institute for Health and Care Excellence (NICE) quality standards for delirium in adults.⁵⁶ The Society of Critical Care Medicine's 2013 Pain, Agitation and Delirium (PAD) guideline outlines a multifaceted approach to the management of delirium in the ICU setting in which the Awakening and Breathing Coordination, Delirium monitoring/management and Early exercise/mobility (ABCDE) care bundle are used.^{42, 43} The ABCDE care bundle includes strategies such as frequent assessment of delirium using a validated tool, treating pain with appropriate analgesia, minimising sedation, implementing sedation breaks and encouraging spontaneous breathing trials and early mobilisation.^{42, 43, 57} The PAD guideline also provides an acknowledgement that

delirium management in the ICU setting has not been adequately studied and requires further investigation.⁴³

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Pharmacological interventions

Pharmacological agents used to manage delirium aim to reduce the severity and duration of the delirium episode while preventing the harmful sequelae.⁵⁸ Like any pharmacological agent, the effectiveness and harms of the agent need to be taken into consideration in determining a suitable treatment agent, hence it is imperative that clinicians are cognisant of any adverse effects that may emerge.²⁵

Pharmacological agent induced harms or adverse effects are unfavorable outcomes that can be detrimental to recovery and may add a financial burden to the health care system.⁵⁹ Not every pharmacological agent is suitable for every patient. Likewise, postoperative cardiac surgical patients require careful consideration due to the myocardial dysfunction and conduction irritability that often presents following cardiac surgery.⁶⁰ Conduction irritability and myocardial dysfunction occurs as a result of reperfusion to the heart and there are large fluid shifts and inflammation that may lead to haemodynamic instability in the initial postoperative period.^{60, 61} Postoperative cardiac patients are reliant on adequate cardiac output.⁶¹⁻⁶³ Low cardiac output impairs cardiac performance leading to tissue and cerebral hypoperfusion and multiorgan dysfunction, increasing the risk of death.⁶⁰⁻⁶⁴

A number of studies have investigated the effectiveness of various pharmacological interventions that include adrenergic alpha-2 agonists (e.g., dexmedetomidine, clonidine), sedatives (e.g., propofol and benzodiazepines e.g., diazepam, midazolam) and typical and atypical antipsychotics (e.g., haloperidol, quetiapine and olanzapine) and have shown mixed results.²³ Randomised controlled trials (RCTs) have investigated the effectiveness of dexmedetomidine in the prevention of postoperative delirium in adult patients after cardiac surgery.⁶⁵⁻⁷⁰ Prophylactic low dose dexmedetomidine (i.e. 0.1micrograms/kg/hr started intraoperatively) as a continuous infusion in the treatment group resulted in significant decreases in the occurrence of delirium after surgery during the first seven days.⁶⁹ Another RCT comparing dexmedetomidine with propofol sedation in reducing delirium after cardiac surgery showed that dexmedetomidine sedation reduced the incidence, delayed the onset and shortened the duration of the delirium episode.⁶⁶ Other pharmacological agents explored include a study comparing ondansetron with haloperidol for the treatment of delirium following cardiac surgery, showing that both ondansetron and haloperidol had good delirium controlling effect but lacked statistically significant differences.⁷¹ Many of these primary studies evaluated the benefits of two pharmacological interventions or a placebo but excluded the assessment of pharmacological harms, adverse or unintended side effects.

1.10 Scope and state of current literature on the topic

A preliminary search of the *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane Library, PubMed, EPISTEMONIKOS and PROSPERO found that there are existing systematic review protocols and finalised systematic reviews on the effectiveness of pharmacological interventions for the treatment of delirium in adult patients in ICUs.⁷²⁻⁷⁸ The focus of many of these published systematic reviews has been on preventing postoperative delirium through the preoperative or perioperative administration of pharmacological agents rather than treatment of postoperative delirium.^{74, 78, 79} One published systematic review examined both prevention and treatment of delirium in the postoperative cardiac surgical patient and found inconclusive evidence to support the treatment of delirium using pharmacological agents.⁷⁵ These reviews have not used the exact inclusion criteria, search strategy or critical appraisal and synthesis approaches that were used in this systematic review. Nor have they systematically examined both effectiveness and harms using standardised appraisal tools. The reporting in these reviews was found to be incomplete where benefits of the intervention were emphasised while the assessing and reporting of harms was inadequately reported.^{74-76, 78-80}

1.11 Relationship between the existing literature and rationale for conducting the systematic review

Well conducted clinical trials and systematic reviews provide the best available evidence for clinicians to identify the most suitable pharmacological agent for their patient. The preliminary search identified poor reporting about harms associated with pharmacological agents used in the treatment of delirium following cardiac surgery. The systematic review that underpins this thesis differed from previously published reviews as it examined both effectiveness and harms using standardised appraisal instruments. Additionally, it was more comprehensive in primary and secondary outcomes compared with previously published reviews.^{72, 75-77, 81, 82} Therefore, the aim was to address the poor reporting about harms and provide a balanced review of both effectiveness and harms related to the pharmacological agents used to treat postoperative cardiac surgical delirium so that clinicians are better informed when treating delirium in this cohort of patients.

In this chapter the topic of interest, the effectiveness and harms of pharmacological interventions in the treatment of delirium in adults treated in the ICU following cardiac surgery were introduced. This chapter also contained an overview of the existing literature with a rationale for conducting a systematic review. In the next chapter EBHC, evidence synthesis and systematic review methodology are introduced.

CHAPTER 2: METHODOLOGY

In this chapter of the thesis the methodology used in the systematic review is introduced. An overview of evidence-based healthcare (EBHC) and the Joanna Briggs Institute (JBI), including its model of EBHC is provided. Following this, there is a discussion on evidence synthesis and the systematic review, Levels of Evidence, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Evidence-based healthcare (EBHC)

The origins of evidence-based practice extend back to the mid-19th century, Paris.⁸³ During this time Pierre Louis (1787-1872), a meticulous clinician, 'pre-formal' epidemiologist and researcher became an important precursor of modern epidemiology and evidence-based practice when he undertook the first known experiment of early bloodletting for the treatment of pneumonia.^{84, 85} Louis understood the importance of sharing his findings, publishing several monographs during his career.⁸⁵ This work was further developed by James Lind (1716-1794), a Scottish surgeon who conducted the first systematic clinical trial looking into the cause and treatment of scurvy in British sailors.⁸⁶ Like Louis, Lind was a prolific writer, sharing his research findings in a bid to seek understanding and change practice as a result.⁸⁶ During the 20th century this work continued and in 1991 David Sackett and his team at McMaster University, Canada coined the term 'evidence-based medicine'.⁸⁷

Evidence-based medicine (EBM) is defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of the patient"^{83(p.71)} An increasing awareness of the weaknesses of standard clinical practices and their impact on both quality and cost of patient care was the impetus for EBM.⁸⁷ Clinical decision-making was once derived through expert opinion, experience and authoritarian judgement.⁸⁷ This novel approach was to bring more certainty to clinical decision-making and to help doctors find the information to ensure that they provide optimal management for their patients.⁸⁸ The practice of EBM involved integrating individual clinical expertise with the best available external clinical evidence from systematic research.⁸³ Clinical expertise referred to the proficiency and judgement of practicing clinicians while external clinical evidence referred to a wide variety of relevant research "that can inform , but can never replace, individual clinical expertise."^{83(p.72)} "It is the clinical expertise that decides whether the external evidence applies to the individual patient and if so, how should it be integrated into a clinical decision".^{83(p.72)}

The primary roots of EBM were originally grounded in medicine, as EBM evolved so to have the professional standards of other health disciplines whose practices are now based on the best available evidence.⁸⁹ Nursing was no exception. During the 1980s, nursing became a professional entity that saw nurse training move from a hospital-based to a university-based education programme. At this time, research utilisation was incorporated into the nursing profession that focused on translating research findings into clinical practice.⁸⁹ To prepare nurses for professional practice, education standards at baccalaureate, master's and doctoral level all required the integration of best evidence, clinical judgment, interprofessional perspectives, and the patient's preferences research.⁸⁹ This led to the evolution of EBM into the EBHC model where it has been utilised by other health disciplines with the aim to provide healthcare that is supported by evidence.⁸⁹

Contemporary understandings of EBHC are based on the need for all health practitioners to practice in ways that are supported by the most up-to-date evidence or knowledge available.⁹⁰ Accessing the best available evidence to assist in clinical decision-making regarding the care of individual patients or the delivery of healthcare services is the fundamental basis of EBHC. All clinical decisions should be based on the best available evidence, the individual patient preference, the context in which the care is being delivered and the professional judgement and expertise of the health clinician.⁹⁰

Evidence is a complex connotative concept with multiple meanings.⁸³ When applied to healthcare, evidence may be defined as "the basis of belief; the substantiation or confirmation that is needed in order to believe that something is true".⁹⁰ The most reliable type of evidence is evidence that has been generated by either quantitative or qualitative research.⁹¹ Quantitative research seeks to establish a relationship between two or more variables with the strength and significance of those relationships being assessed using statistical models.⁹¹ The strength of the quantitative evidence lies in its validity and reliability; results must be repeatable and consistent, yielding the same results or answers time after time.⁹¹ On the other hand, qualitative research takes a humanistic approach that seeks to analyse the human experiences and cultural and social phenomena.⁹¹ Qualitative research incorporates a range of qualitative research methods such as ethnography, phenomenology, qualitative inquiry, action research, discourse analysis and grounded theory.⁹¹

Determining the 'best available evidence' remains controversial as not all evidence is the same.⁹² The hierarchy of evidence pyramid, a core principle of EBHC places the highest form of evidence at the top of the pyramid.⁹² Traditionally, systematic reviews are considered the highest form of evidence while randomised controlled trials (RCTs) are considered to be the 'gold standard' that offers the best approach to generate evidence of effectiveness.⁹² Systematic reviews offer the highest form of evidence as they aim to provide an unbiased, comprehensive and rigorous analysis of all available evidence.^{91, 93} Randomised controlled trials hold their position by the nature of 'randomisation', reducing the risk of bias and examining cause-and-effect

relationships between interventions and outcomes.⁹³ Sackett et al, 1996 argued that reviewing evidence for EBM requires a bottom up approach, an approach that integrates the best external evidence with individual clinical expertise and patients' choice. ^{83(p72)} Since this time, a number of organisations involved in the development and dissemination of evidence-based research and reviews have been established. Organisations such as the JBI, Cochrane Collaboration and Campbell Collaboration have been established to assist health professionals to improve health outcomes by providing the best available evidence to inform clinical decision making.⁹³

The JBI approach to EBHC

The JBI takes an inclusive approach to what constitutes evidence, being that of feasibility, appropriateness, meaningfulness and effectiveness of healthcare practice (FAME).⁹¹ The JBI regard the “findings” of qualitative research studies, text derived from opinion, experience and expertise can also be regarded as the “best available” evidence.”^{91(p.211)} The Institute’s unique approach to EBHC was first published in 2005 as a conceptualised framework that aimed at improving health outcomes.⁹¹ This framework is referred to as the JBI Model of EBHC (referred to hereafter as the ‘JBI Model’).⁹¹ The JBI model is based on the Institute’s approach to translating the best available evidence into best practice in the appropriate healthcare setting. ⁹⁰,
⁹⁴ A recent update of the JBI Model was undertaken in 2016 and is presented in Figure 1.⁹⁵



Figure 1: The JBI Model

The JBI Model is a cyclical process.^{91,95} The 'Central Circle' of the model denotes the 'Pebble of Knowledge', a conceptualisation of EBHC that seeks evidence from the literature to answer questions on feasibility, appropriateness, meaningfulness and effectiveness of a specific intervention for a particular condition.⁹⁵ The five 'Inner Wedges' depict component parts of the JBI Model that include: global health, evidence generation, evidence synthesis, evidence transfer and evidence implementation.⁹⁵ Global health care needs are identified by clinicians or patients/consumers.⁹⁵ Evidence that is feasible, appropriate, meaningful and effective is then generated to address those needs identified.⁹⁵ That evidence is then collated where the results are appraised, synthesised and transferred to the healthcare setting where it can be utilised by health professionals to improve health outcomes, health systems and professional practice.⁹⁵ The 'Outer Wedges' depict the operational components of the JBI Model.⁹⁵ The focus of this thesis is on quantitative evidence and sits within the evidence synthesis wedge as it involves the conduct of a systematic review on the effectiveness and harms of pharmacological interventions in the treatment of delirium in adults in intensive care units post cardiac surgery.

Evidence synthesis

According to the JBI Model, evidence synthesis is defined as "the evaluation or analysis of research evidence and opinion on a specific topic to aid in decision-making in healthcare".^{90(p.211)} Informing practice requires a review of all relevant evidence to be undertaken, where the results are collated, conclusions are drawn upon and recommendations are made.⁹⁰ There have been fourteen types of reviews identified so far with the most common being literature reviews, scoping reviews and systematic reviews.^{96 97} While they all have their merits, literature reviews provide an examination of recent or current literature that covers a wide range of subjects at various levels of completeness and comprehensiveness.⁹⁶ Scoping reviews provide a preliminary assessment of the potential size and scope of available research literature and aims to identify the nature and extent of research evidence.⁹⁶ Systematic reviews remain the core of evidence synthesis; they are essentially a summary of knowledge and a collation of the findings about a specific question/s.^{90, 96}

The systematic review

By definition, "systematic reviews critically appraise and formally synthesise the best existing evidence to provide a statement of conclusion that answers specific clinical questions."^{98(p. 2761)} The nature of the clinical question will determine the type of evidence the systematic review will consider: quantitative, qualitative, mixed methods, an evaluation of health economics or textual evidence.⁹¹ It is generally accepted that systematic reviews follow seven steps:

1. Research question: Formulating the research question that summarises the objective of the review is the first step.⁹¹ For quantitative reviews, the research question identifies the inclusion criteria for

considering studies and should make reference to the review's intended population, intervention, comparator and outcomes (PICO).⁹¹

2. Research protocol: Once the research question has been generated, the research protocol is developed⁹¹. The protocol pre-defines the objectives and methods of the systematic review, outlining the approach for which the review will be conducted and reported and allows for transparency of the review process.⁹¹ Once developed, ideally the protocol is then subjected to peer-review prior to the commencing the review.⁹¹ A requirement of a JBI systematic review is an *a priori* published protocol.⁹⁹
3. Comprehensive search strategy: The literature search aims for exhaustive, comprehensive searching to identify all research relating to the review question.⁹¹ The JBI approach aims to identify both published and unpublished records utilising a three-stage search process.⁹¹
4. Critical appraisal: The aim of a systematic review is to synthesise the best available evidence; hence the methodological quality of included studies needs to be appraised using validated checklists or tools to assess for biases.⁹¹ Quality assessment is undertaken by two independent reviewers to determine inclusion/exclusion of studies.⁹¹
5. Data extraction: Details regarding the participants, interventions, comparators and outcomes are extracted from the included studies.⁹¹ Use of a standardised extraction tool aims to minimise errors in extracting data.⁹¹
6. Data synthesis: Involves the analysing of results, which can either be descriptive (narrative summary) or statistical (meta-analysis).⁹¹ A meta-analysis can be conducted when results of similar (homogeneous) individual studies are combined to determine an overall effect of a particular intervention.⁹¹ A meta-analysis permits a summary about the effect size of an intervention compared to a control.⁹¹ However, when there is diversity or variation (heterogeneous) between the primary studies a narrative summary is provided, including the reasons of the heterogeneity and the inappropriateness of combining the data statistically.⁹¹ The method of data synthesis will always influence the findings of the systematic review.⁹¹
7. Interpretation of results: Data can then be analysed and interpreted, including the strengths and weaknesses of the included studies.⁹¹ The method of data synthesis will always influence the findings of the systematic review.⁹¹ Conclusions should be based on the available evidence, and recommendations for practice and future research are provided at the end.⁹¹

The aforementioned steps of conducting a systematic review are generally accepted across the systematic review community.^{90, 100} The Cochrane Collaboration and the JBI methodology are predominantly used to conduct quantitative systematic reviews for the effectiveness of an intervention.^{90, 100} Systematic reviews are often referred to when decisions around clinical practice are required.⁹⁰ However, there are limitations

associated with conducting a systematic review, such as the time and resources it takes to complete a review. Despite the best efforts of investigators, the evidence and recommendations contained within the review may be outdated by the development and publication of new evidence during this process. In addition, systematic review are by nature focused so that they address very narrow clinical questions and may not assist clinical decision making as a result.⁹⁰

Levels of evidence and the grading of recommendations

Systematic reviews provide a comprehensive summary of the evidence that addresses a clinical question and are considered to be the highest level of evidence. However, evidence is required to be ranked according to its quality and deciphering the quality of the evidence can be challenging and complex. There are a number of hierarchy (pyramid) systems available that focus on placing the highest quality study designs at the top with the weakest at the bottom.⁹² Nevertheless, guidelines are inconsistent on how they rate quality of evidence and grade strength of recommendations.¹⁰¹

In the early 2000s, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group was established.⁹² This working group developed a grading of evidence and recommendation system (referred to as the GRADE approach) that was launched in March 2014 and has since been endorsed by many EBHC organisations.^{102, 103} The GRADE approach is not solely focused on study design but takes into consideration numerous other factors, an approach which challenges the pyramid concept.¹⁰² This approach assists in collating the results of quantitative research, rating the quality of evidence for outcomes and clearly presenting the results in an evidence table, such as a Summary of Findings table (SoF). The factors that GRADE considers include risk of bias, inconsistency, indirectness, imprecision, publication bias, effect sizes, dose-response relationships and confounders of findings (Table 1).¹⁰² The included evidence in the systematic review is then ranked out of a possible four levels (High, Moderate, Low and very Low) (Table 2).¹⁰² The evidence is initially pre-ranked according to the study design; high quality for RCTs and low quality for observational studies ¹⁰²

Table 1: Application of GRADE quality of evidence in the GRADE approach

Quality	Rating quality of results/findings
Risk of bias	Assessed based on the limitations in study design to downgrade the quality of evidence for the outcome into: (a) Not serious (b) serious (c) very serious
Inconsistency	Assessed based on the results being consistent enough across the studies to downgrade the quality of evidence into: (a) Not serious (b) serious (c) very serious
Indirectness	Assessed based on whether the evidence directly answers the healthcare question asked being enough to downgrade the quality of the evidence for the outcome into: (a) Not serious (b) serious (c) very serious
Imprecision	Assessed based on the results being precise or not enough to downgrade the quality of evidence for the outcome into: (a) Not serious (b) serious (c) very serious
Publication bias	Assessed based on the probability of publication bias serious enough to downgrade the quality of evidence for the outcome into: (a) Undetected (b) strongly suspected
Large effect	Assessed based on the magnitude of effect being large or very large, and if so to upgrade the quality of evidence for the outcome into: (a) No (b) large (c) very large
Plausible confounding	Assessed based on the evidence found of studies that the influence of all plausible residual confounding would reduce a demonstrated effect or suggest a spurious effect to either downgrade or upgrade the quality of evidence for the outcome into: (a) No (b) would reduce a demonstrated effect (c) would suggest a spurious effect
Dose response gradient	Assessed based on the presence of evidence of dose-response gradient upgrade the quality of evidence for the outcome into: (a) No (b) yes

***Table taken from the GRADE Handbook, available at <https://gdt.gradepr.org/app/handbook/handbook.html>

Table 2: GRADE ratings and their interpretation

Symbol	Quality	Interpretation
⊕⊕⊕⊕	High	We are very confident that the true effect lies close to that of the estimate effect.
⊕⊕⊕○	Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕○○	Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
⊕○○○	Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

***Table taken from the GRADE Handbook, available at <https://gdt.gradeapro.org/app/handbook/handbook.html>

The evidence can then be either downgraded or upgraded based on the aforementioned factors.¹⁰² Downgrading occurs as a result of risk of bias, inconsistency, indirectness of evidence, imprecision of results and publication bias.¹⁰² Upgrading occurs as a result of large magnitude of effect, dose response and plausible confounding factors.¹⁰² Synthesising the findings pertaining to systematic reviews of effectiveness is presented in a SoF table, which is created from the GRADEpro website (<http://gradeapro.org>).

In this chapter, the methodology used in the systematic review was introduced. An overview of EBHC and JBI, including its model of EBHC was provided. Following this, there was a discussion on evidence synthesis and the systematic review, Levels of Evidence, and the GRADE approach. The next chapter outlines the systematic review methods including eligibility criteria, search strategy, study selection, critical appraisal, data extraction and data synthesis methods.

CHAPTER 3: SYSTEMATIC REVIEW METHODS

The systematic review methods are outlined in chapter three including the review eligibility criteria, search strategy, study selection process, how the studies were critically appraised, data extraction and data synthesis methods. This systematic review was conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence⁹¹ and in accordance with an a priori protocol.⁹⁹ (PROSPERO Registration Number: CRD42018100124).

Inclusion criteria

Types of participants

This review included participants who were adults older than 16 years, who were treated in a cardiothoracic ICU following cardiac surgery and who were identified as having delirium during their postoperative recovery period. This was regardless of ethnicity, gender and with or without co-existing psychiatric or neurological conditions. Cardiac surgery included any type of cardiac surgery (such as, but not limited to, coronary artery bypass [CABG], valvular repairs/replacements and transcatheter aortic valve implantation [TAVI]).

Types of intervention

Studies in which any pharmacological intervention for the treatment of delirium in adult patients treated in the ICU after cardiac surgery was evaluated were considered. Studies that reported any pharmacological intervention were considered for inclusion regardless of dosage, intensity or frequency of administration. The pharmacological interventions considered for inclusion were: atypical and typical antipsychotics such as, but not limited to haloperidol, quetiapine and olanzapine, benzodiazepines such as, but not limited to diazepam and midazolam, sedatives such as, but not limited to propofol and alpha-agonists such as, but not limited to dexmedetomidine and clonidine.

Comparator

Studies that compared the intervention with any other pharmacological intervention for the treatment of delirium in patients who were treated in the ICU after cardiac surgery from the previously mentioned classes of drugs were considered. No limitations were placed on drug classification, dosage of the medications, intensity or frequency of administration.

Outcomes

Studies that included any number of the following primary or secondary outcomes were considered:

Primary outcomes:

- Mortality due to all causes (ICU mortality and post discharge mortality such as but not limited to 30-day mortality)
- Duration of delirium regardless of the measurement approach used
- Severity of delirium regardless of the assessment approach or tools used
- Frequency of the use of physical restraints
- Patients' quality of life during ICU stay as reported by healthcare professionals or family members, regardless of the assessment approach or measurement tools used
- Family members' satisfaction with delirium management provided regardless of the assessment approach or measurement tools used
- The duration and severity of patient aggressive or violent episodes against healthcare staff, other patients and family members or other persons in contact with the patient, regardless of the assessment approach or measurement tools used
- The number and severity of patient falls regardless of the assessment approach used
- The number and severity of patient accidental self-harm events such as but not limited to unintentional extubations, accidental removals of invasive lines, catheters/cannulas regardless of the assessment approach used
- Harms related to pharmacological interventions such as, but not limited to adverse events and side effects, regardless of the assessment approach used
- Harms related to 'over sedation' such as prolonged time to rouse when sedative medications are ceased, wean from mechanical ventilation and be deemed ready for discharge from ICU, regardless of the assessment approach used
- For the purposes of this systematic review, the term 'harms' refers to the totality of all possible consequences of an intervention or therapy such as side effects, adverse events, adverse reactions, adverse drug reactions etc., as defined in the CONSORT Statement: the Statement extension for harms.¹⁰⁴ Harms are the direct opposite of benefits, for which they must be compared against.¹⁰⁵
(p.782)

Secondary outcomes:

- ICU length of stay - number of days from admission to time of discharge from ICU
- Length of hospital stay after ICU discharge – number of days from the time of discharge from ICU to the time of discharge from the hospital
- Total hospital length of stay – number of days from admission to time of discharge from the hospital
- Need for additional medication used for management of the delirium regardless of the approach used for the assessment for the need, otherwise referred to as rescue therapy or medication that is additional to the pharmacological agent being trialed
- Use of additional medication for the management of delirium regardless of the approach used for the assessment for the use. This refers to the need for additional doses of the pharmacological agent being trialed

Types of studies

Both experimental and non-experimental study designs were considered such as RCTs, non-RCTs, quasi-experimental, before and after studies, observational, prospective and retrospective cohort studies and analytical cross-sectional studies for inclusion. We considered for inclusion firstly randomized experimental studies as they provide, by randomization, for both effectiveness and harms, less biased evaluations of effects compared to other study designs. In the absence of randomized experimental studies, we considered non-randomized controlled trials and quasi-experimental studies. In the absence of experimental and quasi-experimental studies we would have considered analytical observational studies.

Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was used. An initial limited search of PubMed and CINAHL was undertaken, followed by analysis of the text words contained in the title and abstract and the index terms used to describe the articles. A second search using all identified keywords and index terms was undertaken between the 21st and 25th September 2017. Thirdly, the reference lists of all citations retrieved for full text screening were searched for additional studies prior to their appraisal. Only studies published in English were considered for inclusion in this review. There was no date limit or geographical restrictions on the search strategy. The search was repeated on the 18 November 2018 to verify currency.

To ensure that the search was extensive an additional hand search of journals relevant to the specialised topic was undertaken. The journals selected were determined by the review team and based on the most commonly accessed national and international intensive care and cardiothoracic journals by clinicians. An

initial time limit of five-years (2012 – 2017) was set for the initial hand search, with a repeat search carried out from September 2017 until September 2018. This gave an overall hand search period of six years. The decision to limit the number of journals and time period for hand searching was based on the limited availability of resources. A research librarian assisted throughout this process. The full search strategies are presented in Appendix I.

Information sources

The databases searched were:

- PubMed
- Embase
- CINAHL
- Web of Science
- Cochrane Central Register of Controlled Trials
- Scopus
- EPISTEMONIKOS.

The search for unpublished studies included:

- Australian New Zealand Clinical Trials Registry
- ClinicalTrials.gov
- Clinical Trials in New Zealand
- ProQuest Dissertation and Theses.

A hand search for primary studies published in relevant journals (2012 – 2018) for the last six years included:

- Australian Critical Care
- Journal of Cardiothoracic Surgery
- American Journal of Respiratory and Critical Care Medicine
- Intensive Care Medicine
- Critical Care Medicine

A hand search for primary studies used in relevant clinical practice guidelines included:

- American Society of Critical Care Medicine
- American Society of Critical Care Nurses
- Australian and New Zealand Society of Critical Care Medicine.

Study selection

Following the search, all identified citations were loaded into EndNote X7 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria. The full text of potentially eligible studies was retrieved and assessed in detail against the inclusion criteria by two independent reviewers. The details of studies that met the inclusion criteria were imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI, The Joanna Briggs Institute, Adelaide, Australia). Full text studies that did not meet the inclusion criteria were excluded and reasons for their exclusion are provided in Appendix II. Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

Assessment of the methodological quality

As originally outlined in the review protocol,⁹⁹ eligible studies selected for retrieval were critically appraised by two independent reviewers at the study level using the standardised critical appraisal instrument from JBI for RCTs.⁹³ The McMaster Quality Assessment Scale of Harms (McHarm) for primary studies was also used to appraise the quality of the studies exploring the pharmacological harms, adverse or unintended effects.¹⁰⁵¹⁰⁶ Studies were included regardless of methodological quality. There were no disagreements between the two reviewers therefore a third reviewer was not required.

Data extraction

Data was extracted from studies included in the review by two independent reviewers, using the standardised JBI data extraction tool.⁹³ The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and objective. There were no disagreements between the two reviewers therefore a third reviewer was not required.

Data synthesis

A meta-analysis was not performed as there were significant differences between interventions and outcome measures (clinical heterogeneity) and designs (methodological heterogeneity). Thus, the findings have been presented in narrative form, including tables to aid in data presentation.

Assessing certainty in the findings

The GRADE approach for grading the certainty of evidence was followed¹⁰⁷ and a Summary of Findings (SoF) was created using GRADEPro GDT 2015 (McMaster University, ON, Canada). The SoF presents the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The primary outcomes reported in the SoF include mortality,

duration, severity or presence of delirium, harms related to pharmacological interventions and hospital/ICU length of stay (LoS).

In this chapter the methods used in the underlying systematic review were outlined, including the eligibility criteria, search strategy, study selection process, how the studies were critically appraised, data extraction and data synthesis methods. In the next chapter, the search results, reasons for excluding studies, assessment of the methodological quality and an overview of the results of the three papers included in the systematic review is provided.

CHAPTER 4: RESULTS

In chapter four, the findings of the systematic review conducted to evaluate the effectiveness and harms of pharmacological interventions in the treatment of delirium following cardiac surgery are provided. A detailed description of the search results, the study selection process and the assessment of methodological quality is presented which is followed by the characteristics of the included studies. Finally, a narrative synthesis of the results organised by outcome is provided.

Description of search results and study selection process

The initial search was undertaken in September 2017 and identified a total of 3201 potentially relevant citations using the search strategies developed for each database (Appendix I), plus 227 records identified through other sources. The search was updated in November 2018 and limited to 12 months, which identified 1019 potentially relevant citations. Between the two search dates, a total of 4447 records were identified. Of the 4447 citations, 430 were excluded as duplicates. Of the remaining citations, 3802 were excluded after examination of the title and abstract. A full-text review of 215 papers was conducted, 205 were immediately excluded for not fulfilling the inclusion criteria (reasons for exclusion are presented in Appendix II). The remaining 10 studies were then assessed by two independent reviewers. One RCT was subsequently excluded on the basis of treating subsyndromal delirium rather than hyperactive delirium.¹⁰⁸ One abstract and five studies were excluded due to higher-quality studies being located,^{3,109-113} One cohort study¹⁰⁹ was identified as a precursor to an included RCT.⁷¹ The methodological quality of the remaining three studies was assessed, and the studies were subsequently included in this review. See Figure 1 for the described process.¹⁰⁵

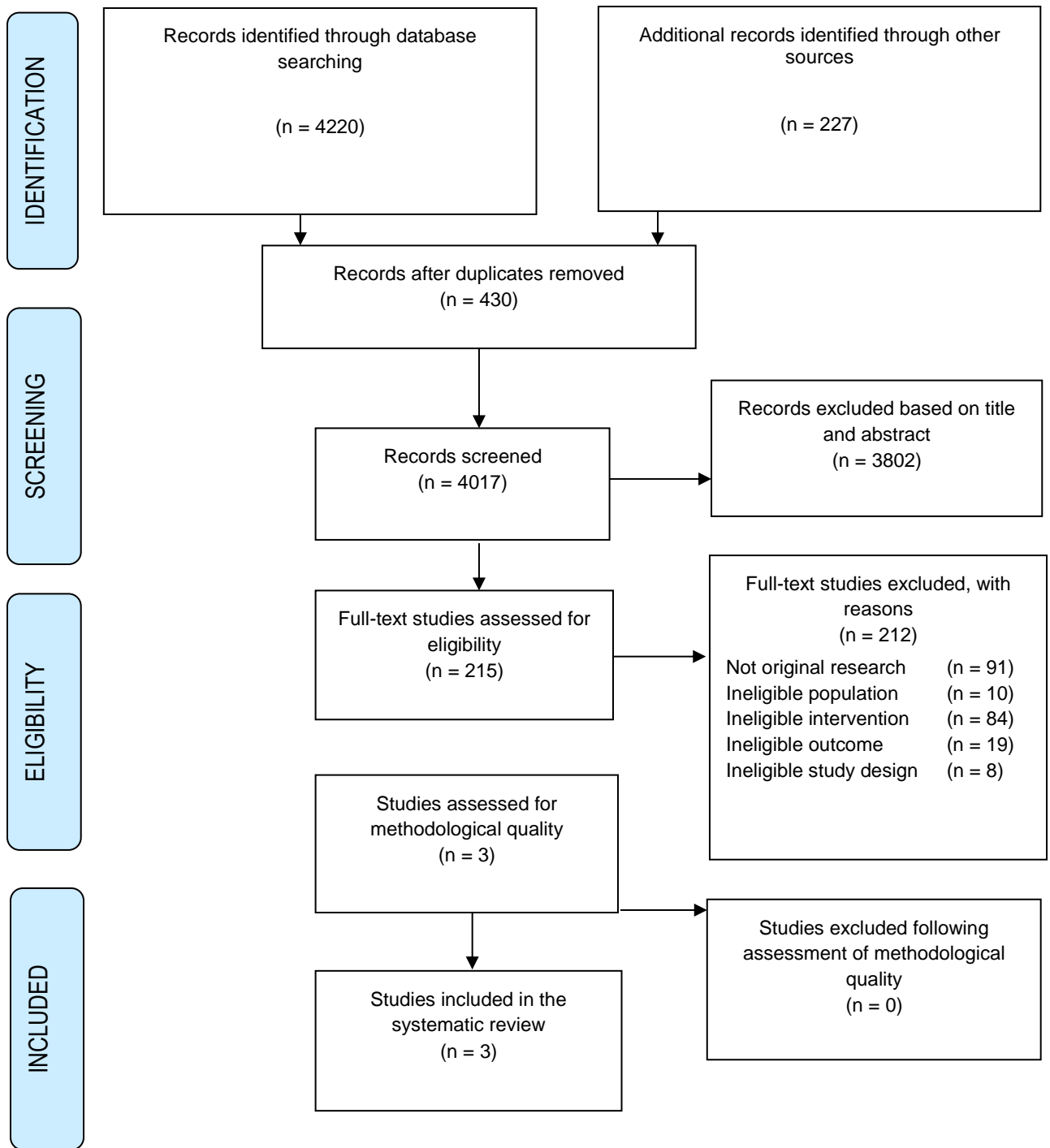


Figure 2: PRISMA Flowchart of the study selection and inclusion process ¹⁰⁵

Methodological quality of included studies

Two independent reviewers carried out critical appraisal of the three included studies using the JBI critical appraisal tool for RCTs.⁹³ The JBI critical appraisal tool contains thirteen questions. Responses are either a yes, no or unclear. Across the three studies the majority of responses were 'unclear' (n=28), the remainder were 'yes' (n=11) signifying low methodological quality (Table 3). The low methodological quality occurred mainly as a result of information lacking related to true randomisation, allocation concealment, blinding of participants, clinicians and assessors, follow-up, intention-to-treat analysis, reliability of measured outcomes and statistical analysis procedures where information was unclear for all three studies. For example, the study design in two studies was reported as 'randomized with participants randomly allocated into two groups'^{70, 71} while the third study was reported as a 'prospective, randomized, double-blinded study'¹¹⁴ however no details regarding the actual procedure for randomisation were provided. This may have impacted the internal validity of the studies or the authors simply omitted these details in their published papers. Efforts to elicit further information by contacting each of the authors (n=6) directly to request missing or additional data was unsuccessful.

Table 3: Critical appraisal results of eligible studies using the JBI Critical Appraisal Checklist for Randomised Controlled Trials

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Atalan et al. ¹¹²	U	U	Y	U	U	U	Y	U	U	Y	U	U	Y
Tagarakis et al. ⁷¹	U	U	Y	U	U	U	U	U	U	Y	U	U	Y
Yapici et al. ⁷⁰	U	U	Y	U	U	U	Y	U	U	Y	U	U	Y
Total number Y	0	0	3	0	0	0	2	0	0	3	0	0	3

Y = Yes; N = No; U = Unsure; JBI Critical appraisal checklist for randomized controlled trials: Q1 = Was true randomization used for assignment of participants to treatment groups?; Q2 = Was allocation to treatment groups concealed?; Q3 = Were treatment groups similar at baseline?; Q4 = Were participants blind to treatment assignment?; Q5 = Were those delivering treatment blind to treatment assignment?; Q6 = Were outcome assessors blind to treatment assignment?; Q7 = Were treatment groups treated identically other than the intervention of interest?; Q8 = Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?; Q9 = Were participants analyzed in the groups to which they were randomized?; Q10 = Were outcomes measured in the same way for treatment groups?; Q11 = Were outcomes measured in a reliable way?; Q12 = Was appropriate statistical analysis used?; Q13 = Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

The McMaster Quality Assessment Scale of Harms (McHarms) appraisal tool contains fifteen questions to guide the appraisal of harms data collection and reporting.^{105, 106} The MCHarms appraisal tool insures harms reporting in RCTs meets the standards and recommendations defined in the CONSORT Statement: the Statement extension for harms.¹⁰⁴ The questions relate to assessing if harms were pre-defined using standardised definitions, if serious or severe events occurred, if deaths occurred, how the harms data was collected, who collected the harms data and their training in harms data collection, the timing and frequency of harms data collection, what harms data collection tools were used as well as follow-up. Responses were either 'yes', 'no' or 'unclear'. For all three studies the majority of responses were 'no' (n=41), only two were

'yes' (n=2) with the remaining two 'unclear' (n=2) signifying that the overall quality of harms reporting was low (Table 4).

Only one study¹¹⁴ reported the number of deaths in each study arm,¹¹⁴ however no further details were provided relating to the cause of the deaths. In the other two studies, mortality rates were not provided and reasons for excluding this information were not provided. Yapici et al. was the only study that reported the timing and frequency of data collection. However, it was difficult to substantiate if the timing and frequency of data collection was an a priori intention to monitor and report harms. Appraisal of the studies revealed that the study publications did not clearly report the methods of identifying harms, the incidence of the harms or potential harms related to the study methodology or interventions. In all three studies, no information was provided relating to using standardised pre-defined harms definitions, seriousness of events, mode of harms data collection (active or passive), who collected the data, assessor training or background, standardised data collection checklists, or what events were considered to be drug related harm. Additionally, efforts to elicit further information by contacting the authors was unsuccessful.

Table 4: Critical appraisal results of eligible studies using the McMaster quality assessment scale of harms (McHarms) critical analysis

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
Atalan et al. ¹¹⁴	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
Tagarakis et al. ⁷¹	N	N	N	N	U	N	N	N	N	N	N	N	N	N	N
Yapici et al. ⁷⁰	N	N	N	N	U	N	N	N	Y	N	N	N	N	N	N
Total number Y	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0

Y = Yes; N = No; U = Unsure; McMaster Quality assessment scale of harms (McHarms) critical analysis tool: Q1 = Were the harms PRE-DEFINED using standardised or precise definitions?; Q2 = Were SERIOUS events precisely defined?; Q3 = Were SEVERE events precisely defined?; Q4 = Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?; Q5 = Was the mode of harms collection specified as ACTIVE?; Q6 = Was the mode of harms collection specified as PASSIVE?; Q7 = Did the study specify WHO collected the harms?; Q8 = Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?; Q9 = Did the study specify the TIMING or FREQUENCY of collection of the harms?; Q10 = Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?; Q11 = Did the author(s) specify if the harms reported encompass ALL the events collected or a selected SAMPLE?; Q12 = Was the TOTAL NUMBER of participants that withdrew or were lost to follow-up specified for each study group?; Q13 = Was the TOTAL NUMBER of participants affected by harms specified for each study arm?; Q14 = Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?; Q15 = Did the author(s) specify the type of analyses undertaken for harms data? ¹⁰⁵

Consensus among the reviewers was to include all three studies, despite their low methodological quality both in terms of conduct and reporting. This decision was made as there were a limited number of RCTs that met the inclusion criteria.^{70, 71, 114} No other study designs were included in this review.

Characteristics of the included studies

In this section, we present a narrative synthesis of the characteristics of included studies. Details related to methods, participants' characteristics, interventions, comparators and outcomes reported by the authors are presented in the table of included studies in Appendix III.

Research design

This systematic review included three RCTs.^{70, 71, 114}

Sample size

A total number of 205 participants who were treated for postoperative delirium after cardiac surgery were included. Sample sizes ranged from 53 to 80 participants, with 53¹¹⁴, 72⁷¹ and 80⁷⁰ participants identified in each study.

Setting, publication country and characteristics of study participants

The three included studies were published between 2010 and 2013. The setting, country and city where the included studies were conducted as well as the characteristics of participants, including the mean and standard deviation (SD) of age of the sample by intervention group are presented in Table 5.

Table 5: Characteristics of participants in the included studies

Study	Setting	Country (City)	Characteristics of participants	Age of sample	
				Intervention group Mean \pm SD	Comparator group Mean \pm SD
Atalan et al. ¹¹⁴	ICU of a single community hospital Intervention (M) Group (n=27) Comparator (H) Group (n=26)	Turkey (Istanbul)	Delirious adult patients who had undergone cardiac surgery \pm cardiopulmonary bypass and initially admitted into the ICU.	65.74 \pm 9.67	66.00 \pm 8.39
Tagarakis et al. ⁷¹	ICU and the Department of Cardiovascular and Thoracic Surgery at the University Hospital of Larissa Intervention (O) Group (n=40) Comparator (H) Group (n=40)	Greece (Thessaly)	Adult patients who developed delirium after heart surgery with the application of heart lung-machine, admitted into the ICU.	70.10 \pm 9.30	70.90 \pm 9.90
Yapici et al. ⁷⁰	Adult ICU Intervention (D) Group (n=38) Comparator (M) Group (n=34)	Turkey (Istanbul)	Adult patients who underwent elective coronary artery bypass grafting, valve replacement or both between February 2005 and August 2007 admitted into the ICU and who failed at least one trial of continuous positive airway pressure and had agitation.	58.91 \pm 10.49	61.17 \pm 9.15

ICU = Intensive Care Unit, SD = Standard Deviation.

Table 6 shows the characteristics of intervention (dosage and duration) and comparator for individual studies.

Table 6: Characteristics of the interventions in the included studies

Study	Delirium Assessment Tool	Intervention	Comparator	
Atalan et al. ¹¹⁴	CAM-ICU + RASS sedation score	Patients received 5milligrams of morphine sulphate intramuscularly which was repeated every hour until the adequate sedation and target RASS scores (between -1 and +1) were achieved.	Patients received 5milligrams of haloperidol intramuscularly which was repeated every hour until the adequate sedation and target RASS scores (between -1 and +1) were achieved.	
		Protocol in both groups		
		In patients who were still agitated despite the administration of 20milligrams per day of morphine sulphate or haloperidol, 2.5milligrams of lorazepam per oral, twice a day was added to the treatment regime. All delirious patients were re-evaluated every 12 hours or for a maximum of 10 days following surgery.		
Tagarakis et al. ⁷¹	4-point scale for evaluation of delirium	Patients received 8milligrams of ondansetron intravenously on detection of delirium.	Patients received 5milligrams of haloperidol intravenously on detection of delirium.	
		Protocol in both groups		
		All patients were evaluated before and 10 minutes after the injection with a 4-point scale for the evaluation of delirium. No further details were provided on the treatment procedure used in the study or if any study participants required any additional treatment (either pharmacological or non-pharmacological) other than restraints.		
Yapici et al. ⁷⁰	CAM-ICU	Protocol in both groups		
		Initially, all patients were commenced on a fentanyl infusion (20-50micrograms/kg/hr) and a midazolam infusion (0.05-0.1milligrams/kg/hr) prior to randomisation into the intervention or comparator groups.		
		Patients received a 0.3-0.7micrograms/kg/hr of dexmedetomidine intravenously. After the initiation of the dexmedetomidine treatment, the background sedation of fentanyl and midazolam were weaned off and ceased. The dexmedetomidine dose was titrated based on the patients' heart rate and blood pressure response.	Patients received 0.05-0.2milligrams/kg/hr of midazolam intravenously to control delirium. Some patients in this group received haloperidol 5milligrams intramuscularly 4 times per day for treatment of agitation as well as other drugs such as benzodiazepines, haloperidol or atypical antipsychotics.	
		Protocol in both groups		
		Both groups received nonsteroidal anti-inflammatory drugs or paracetamol for analgesia.		

Abbreviations: CAM-ICU = Confusion Agitation Method for Intensive Care Unit; RASS = Richmond Agitation Sedation Scale.

Outcomes

Primary outcomes

This systematic review examined eleven primary outcomes of interest. Most were not measured or assessed in the included clinical trials, as summarised in Table 7

Table 7: Summary of the measured primary outcomes of the included studies

Primary Outcomes	Atalan et al. ¹¹⁴	Tagarakis et al. ⁷¹	Yapici et al. ⁷⁰
Mortality	Y	N	N
Total duration of delirium	Y	N	N
Severity of the delirium	Y	N	N
Frequency in the use of physical restraints	N	Y	N
Quality of life during ICU stay	N	N	N
Family members satisfaction with delirium management	N	N	N
Duration and severity of patient aggression or violent episodes against healthcare staff, other patients and family members or other persons in contact with the patient	N	N	N
The number and severity of patient falls	N	N	N
The number and severity of patient accidental self-harm events	N	N	N
Harms related to pharmacological interventions	Y	Y	Y
Harms related to over-sedation	N	N	N

Abbreviations: N= not measured, Y = measured and assessed.

Five secondary outcomes of interest were included. Many of those secondary outcomes were not measured in the included clinical trials, as summarised in Table 8.

Table 8: Summary of the measured secondary outcomes of the included studies

Secondary Outcomes	Atalan et al. ¹¹⁴	Tagarakis et al. ⁷¹	Yapici et al. ⁷⁰
ICU length of stay	Y	N	N
Length of hospital stay after ICU discharge	Y	N	N
Total hospital length of stay	Y	N	N
Need for additional medication for delirium management	Y	N	Y
Use of additional medication for delirium management	Y	N	Y

Abbreviations: N= not measured, Y = measured and assessed.

All included studies reported different clinical outcomes and were highly heterogeneous therefore a meta-analysis was unable to be conducted and instead a narrative approach was adopted. The results have been organised in order of primary outcomes (including harms) followed by secondary outcomes.

Primary outcomes

Mortality

Only one study assessed hospital mortality.¹¹⁴ Atalan et al. reported that there was no statistically significant difference in hospital mortality between the morphine treatment group and the haloperidol treatment group (7.7% [2/26] vs. 3.7% [1/27]; $p=0.61$).

Total duration of delirium

Only one study assessed the total duration of delirium.¹¹⁴ Atalan et al. measured the duration of delirium in hours, reporting that there was no significant difference between the morphine group compared with the haloperidol group. The mean duration was 36.0 +/- 16.1 hours (range 12-90 hours) (33.92 +/- 16.70 vs. 31.56 +/- 16.6 [$p=0.607$]).

Severity of the delirium

While the presence of delirium was assessed in all three studies only one study assessed the severity of delirium.¹¹⁴ The screening tools used in these studies to detect the presence of delirium included the Richmond Agitation Sedation Scale (RASS), the Confusion Assessment Method for Intensive Care Units (CAM-ICU)^{70, 114} and a 4-point scale.⁷¹ RASS is a validated and reliable tool used to assess sedation level. This 10-point scale ranges from +4 to -5, where +4 is indicative of signs of agitation, 0 is descriptive of an alert and calm patient, and -5 is indicative of a unresponsive and unarousable patient.¹¹⁵ CAM-ICU is a

validated and reliable tool used to screen for delirium that can be used for either intubated or extubated patients.¹¹⁶ The 4-point scale was developed by Bayindir et al. to detect and evaluate delirium.¹⁰⁹ The 4-point scale rates as follows: 0-normal, 1-patient with restlessness and mild confusion but cooperative, 2-patient is disorientated but cooperative, memory gaps, 3-patient disorientated and uncooperative with augmented mobility that could put the patient in danger, 4-patient totally disorientated, violent and aggressive, presence of hallucinations.¹⁰⁹

Atalan et al. measured delirium severity using the RASS and reported that there was a reduction in severity of the delirium in both the control and intervention groups in conjunction with decreased RASS scores and drug dose over a five-day period. The mean daily doses of morphine on Day 1 was 9.81 mg to 0.0 mg on Day 5 vs haloperidol on Day 1 10.96 mg to 0.28 mg Day 5.¹¹⁴ While Yapici et al. measured and reported the presence of delirium using RASS, no explicit statement was provided regarding measurement of the severity of the delirium experienced by participants. Tagarakis et al. assessed the presence of delirium with a 4-point scale which was used pre and ten minutes after the administration of the treatment drug. There was no explicit statement provided by Tagarakis et al. regarding measuring the severity of delirium however they did report a statistically significant improvement in the test score after the administration of both ondansetron and haloperidol (3.1 +/- 0.4 vs 3.1 +/- 0.4 pre-administration vs 1.2 +/- 0.1 vs 1.3 +/- 0.1 post administration [$p < 0.01$]).

Frequency in the use of physical restraints

One study reported the use of physical restraints.⁷¹ Tagarakis et al. reported that unresolved delirium continued in seven participants included in the ondansetron treatment group and six in the haloperidol treatment group that required restraints and returned to a calm state.⁷¹ However, no additional details were reported on how patients were returned to calmness or how long physical restraints were required.

Harms and Adverse Effects

Assessing the harms of pharmacological interventions in the treatment of delirium after cardiac surgery and how harms were reported in the included clinical trials was a primary outcome of interest for this systematic review.

Harms related to pharmacological interventions

The three included studies provided statements related to harms associated with pharmacological interventions.^{70, 71, 114} Atalan et al. monitored harms related to pharmacological interventions by observation, reporting that no serious or adverse effects were observed in either the haloperidol or morphine treatment

group but provided no additional details.¹¹⁴ Likewise Tagarakis et al. provided a statement that ondansetron was safer with milder side effects compared with haloperidol with no additional details. Yapici et al. measured and monitored heart rate (HR), blood pressure (BP), respiration rate (RR), peripheral capillary oxygen saturation (SpO₂), partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂) and arterial blood gases (ABGs) and reported that they found significantly different HRs between the dexmedetomidine treatment group and the midazolam treatment group but did not observe any haemodynamic side effects. Yapici et al. reported that 50% of the patients with hypotension in the dexmedetomidine treatment group responded successfully to dose titration or the administration of intravenous fluids.⁷⁰

A summary of the harms based on the McHarm appraisal tool is provided in Table 9. Only two of the 15 questions were answered. The primary authors of the included clinical trials were contacted requesting further details of their research but without success.

Table 9: Summary of the reporting of harms using McHarm appraisal tool of the included studies

Harms Question		Atalan et al. ¹¹⁴	Tagarakis et al. ⁷¹	Yapici et al. ⁷⁰
Q1	Were the harms PRE-DEFINED using standardised or precise definitions?	N	N	N
Q2	Were SERIOUS events precisely defined?	N	N	N
Q3	Were SEVERE events precisely defined?	N	N	N
Q4	Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?	Measured and reported the number of deaths in each study group. However, no details were provided on the reasons for the deaths nor were there details on why that information was not provided.	N	N
Q5	Was the mode of harms collection specified as ACTIVE?	N	N	N
Q6	Was the mode of harms collection specified as PASSIVE?	N	N	N
Q7	Did the study specify WHO collected the harms?	N	N	N
Q8	Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?	N	N	N
Q9	Did the study specify the TIMING and FREQUENCY of collection of the harms?	N	N	Reported that the timing and frequency of data related to drug effectiveness was conducted at 0, 6, 12 and 24-hour time points. However, it is difficult to ascertain if this data collection was specific to harms data collection.
Q10	Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	N	N	N
Q11	Did the author(s) specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	N	N	N
Q12	Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	N	N	N
Q13	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	N	N	N
Q14	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	N	N	N
Q15	Did the author(s) specify the type of analysis undertaken for harms data?	N	N	N

Abbreviations: N = not reported

Secondary outcomes

ICU length of stay

One study assessed the total ICU length of stay⁴⁵ in days, reporting that there was no significant difference between the morphine group compared with the haloperidol group. The mean duration was 3.3 days vs 2.8 days (2.85 +/- 1.48 days vs. 3.31 +/- 2.32 [p=0.402]).

Length of hospital stay after ICU discharge

Atalan et al. reported ICU length of stay and the total hospital length of stay. Although there was no explicit statement regarding the length of hospital stay after ICU discharge this can be deduced from both sets of data; mean duration of 5.2 days vs 6.1 days in the haloperidol group compared with the morphine group respectively.

Total hospital length of stay

The total length of hospital stay¹¹⁴ in days was assessed in one study, in which it was reported that there was no significant difference in the morphine group compared with the haloperidol group. The mean duration was 8.5 days vs 8.9 days (8.93 +/- 3.11 days vs. 8.54 +/- 3.44 [p=0.607]).

Need for additional medication for delirium management

This secondary outcome concerned the need for additional (rescue) medication that may have been required in addition to the study pharmacological agent. Two studies included in this systematic review reported the need for additional medication for delirium management.^{70, 114} Atalan et al. reported that lorazepam 2.5mg (orally twice daily) was administered to patients who had received more than 20mg of the treatment drug and remained delirious. Atalan et al. reported that those treated with additional medication to manage unresolved delirium required significantly less additive medication in the morphine treatment group compared with the haloperidol treatment group (one participant vs eight participants). Yapici et al. reported that the midazolam treatment group required the use of additional medications such as benzodiazepines, haloperidol or atypical antipsychotics to manage unresolved delirium. Yapici et al. stated that some midazolam treatment group participants received 5mg haloperidol intramuscularly four times per day for the treatment of excessive agitation. However, no further details were provided. In both studies, there were no explicit statements regarding the clinical judgment used to determine the need for additional medication compared with the actual administration of additional medication, such as the review process including patient assessment or whether non-pharmacological interventions were tried first.

Use of additional medication for delirium management

This secondary outcome concerned the need for additional doses of the pharmacological study agents. Atalan et al. reported that patients in both the morphine and haloperidol groups were administered 5mg of the treatment drug every hour until adequate sedation and a target RASS score of -1 to +1 was achieved. Yapici et al. reported that both the dexmedetomidine and midazolam were titrated to maintain the level of sedation within a predefined range of 10% increases or decreases in infusion rate.

In this chapter the underlying systematic review conducted to evaluate the effectiveness and harms of pharmacological interventions in the treatment of delirium following cardiac surgery was provided. A detailed description of the search results, the study selection process and the assessment of methodological quality was presented which was followed by the characteristics of the included studies. Finally, a narrative synthesis of the results organised by outcome was provided. In the next chapter, the findings and limitations of the systematic review will be discussed, along with the conclusions and the implications for practice and future research in this area.

CHAPTER 5: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS FOR PRACTICE AND RESEARCH

Two objectives are addressed in the final chapter of this thesis. The first objective is to provide an overview of the findings of the review, highlighting the effectiveness of pharmacological interventions on delirium after cardiac surgery as well as the harms of those pharmacological interventions on cardiac function after cardiac surgery. The second objective is to discuss the strengths and limitations of the review before finally concluding with remarks regarding implications of this review for clinical practice and future research.

Overview of findings

Cardiac patients are at increased risk of delirium after cardiac surgery, in which the duration and severity adversely impacts morbidity and mortality.¹¹⁷⁻¹¹⁹ Treating the episode is challenging as there is a lack of knowledge about the exact cause.^{33, 37} The aim of this systematic review was to identify the effectiveness of any pharmacological intervention for the treatment of identified delirium after cardiac surgery in reducing the duration and severity of the delirious episode and to assess the harms associated with those medications.⁹⁹ Only three trials were identified and included in this review (morphine vs haloperidol, ondansetron vs haloperidol and dexmedetomidine vs midazolam).^{70, 71, 114} Two trials indicated that the pharmacological interventions were effective in managing the symptoms of hyperactive delirium after cardiac surgery^{70, 114} while the remaining trial suggests that both ondansetron and haloperidol had “good controlling effects”.⁷¹ The trials were too heterogeneous for a meta-analysis to be performed and therefore a narrative approach was taken.

In all three studies, there were methodological limitations in relation to poor reporting of information related to true randomisation, allocation concealment, blinding, follow-up of participants, intention-to-treat and statistical analysis procedures and small sample sizes. It was also unclear for all three studies, if the outcomes were measured in a reliable and consistent manner as there were no details pertaining to the number of raters, training of raters of delirium or the intra and inter-rater reliability within the studies.

The investigators of the study in which the effectiveness of haloperidol was compared with morphine for the treatment of delirium stated that morphine was found to be a reasonable alternative to haloperidol in the management of delirium following cardiac surgery due to its rapid action and absence of side effects.¹¹⁴ However, critical appraisal of the study revealed significant concerns about potential bias and associated drug harms that may affect this group of patients. Therefore, the findings of the study do not support the adoption of morphine as a treatment alternative for delirium in the postoperative cardiac surgical patient in practice.

In the reporting of harms, Atalan et al. did not outline any predefined harms relating to morphine, the monitoring of potential harms or how harms would be managed, including the management of over-sedation. According to the Food and Drug Association (FDA), the known effects of the opioid antagonist morphine is that it suppresses the central nervous system (CNS) and respiratory drive leading to decreased level of consciousness and rate of breathing, oxygenation and possibly apnoea. Regular monitoring of sedation and delirium was performed in this study, using RASS and CAM-ICU respectively.¹¹⁴ However, details were lacking about monitoring respiratory function and over-sedation or how it was to be managed. Additionally, morphine may cause vomiting, nausea and constipation which was not acknowledged or reported in this study. Mortality rates were reported; however, details were not provided relating to cause of death or follow-up of participants.

In this study, morphine was administered intramuscularly (IM) every hour until a RASS sedation score of -1 to +1 was achieved.¹¹⁴ Morphine is an opioid with excellent analgesic efficacy and euphoric properties, commonly indicated for the management of pain.⁵⁷ Postoperative pain is a known complication after cardiac surgery.^{120, 121} Studies have suggested that postoperative pain is a contributing factor in the development of delirium if not managed effectively.^{120, 121} Opioids, such as morphine are highly effective, inexpensive and can be administered via a number of routes with the peak therapeutic effect varying depending on the route of administration. However, morphine administered IM has been found to have a slower absorption rate and has an unreliable distribution.¹²²⁻¹²⁴ Studies have been conducted comparing intravenously (IV) and IM administered morphine.¹²²⁻¹²⁴ The results revealed that IV administration is superior in terms of a significantly faster onset (5 minutes vs 20 minutes) with improved analgesic effect compared with IM administration.¹²²⁻¹²⁴ This study omitted details pertaining to pain assessment and management, therefore it was difficult to ascertain if the effect was a result of over-sedation to manage the symptoms of hyperactive delirium or pain management as opposed to effectively managing delirium.

Morphine may be contraindicated due to potential complications of bleeding during critical illness.^{122, 124, 125} Morphine is known to cause the release of histamine, which may lead to vasodilation and an increased risk of bleeding (particularly for the surgical patient).^{122, 124, 125} This deleterious effect on a haemodynamically unstable postoperative cardiac surgical patient, may result in decreased heart rate, hypotension, decreased venous return, respiratory depression, nausea, vomiting, constipation, tolerance and physical dependence.^{122, 124, 125} A reduction in opioid use to reduce the risk of over-sedation, delirium and respiratory depression is advocated in the newly released guideline for Pain, Agitation and Delirium, by the Society of Critical Care Medicine.⁵⁷

The Atalan et al. study report was incomplete with regard to effectiveness and harms; therefore, it was difficult to verify if morphine was effective in reducing the severity and duration of the hyperactive delirium or if the deliria symptoms were controlled through sedation. It is also difficult to verify if there were any harms as harms and adverse effects were not reported fully in this trial and there was no follow-up of participants for side effects. Therefore, no conclusions can be made about the findings of this study.

The investigators of the study in which the effectiveness of haloperidol was compared with ondansetron for the treatment of delirium stated that both ondansetron and haloperidol were found to have good controlling effects on delirium following cardiac surgery.⁷¹ However, critical appraisal of the study revealed significant concerns about potential bias and associated drug harms that may affect this group of patients. Therefore, the findings of the study do not support the adoption of ondansetron as a treatment alternative for delirium in the postoperative cardiac surgical patient in practice. In this study, ondansetron was administered once on detection of delirium with screening performed ten minutes following the administration of the medication using an unvalidated tool developed by Bayindir et al.^{71, 109}

Tagarakis et al. did not outline any predefined harms relating to ondansetron, the monitoring of harms or how harms would be managed, mortality or follow-up of participants. There was no information about how data were measured or who collected it, and therefore no details provided relating to severity, duration, frequency of delirium screening, cardiac or electrocardiogram (ECG) monitoring. Furthermore, there were no details provided about the management for ongoing delirium other than additional pharmacological agents and physical restraints.

Ondansetron is a 5HT₃ serotonin receptor antagonist that may cause confusion, anxiety, agitation, depression, restlessness, headaches and insomnia.^{126, 127} Furthermore, the administration of IV ondansetron in patients with a cardiac history although rare, may result in QT prolongation and cardiac arrhythmia.^{126, 127} The reporting was incomplete, so it is difficult to verify if ondansetron is effective for reducing the severity and duration of delirium and whether it is an appropriate choice for delirium management in the postoperative cardiac patient. Therefore, no recommendations can be drawn from the findings of this study.

The investigators of the remaining study in which the effectiveness of dexmedetomidine was compared with midazolam for the treatment of delirium stated that dexmedetomidine may help eliminate the symptoms of delirium and reduce mechanical ventilation times with no haemodynamic compromise.⁷⁰ However, critical appraisal of the study revealed significant concerns about potential bias and associated drug harms that may affect this group of patients. Therefore, the findings of the study do not support the adoption of dexmedetomidine as a treatment alternative for delirium in the postoperative cardiac surgical patient in practice.

Reports of hypotension and bradycardia were documented in this study which were not identified as adverse effects associated with the pharmacological agent.⁷⁰ Dexmedetomidine is a highly selective adrenergic alpha-2 agonist that targets the alpha-2 adrenergic receptors at the pre and postsynaptic terminals producing an analgesic, anxiolytic and sedative effect.¹²⁸ Alpha-2 receptors are located in the CNS and peripheral nervous system (PNS), including smooth muscle tissue.¹²⁸ The responses to activation of the receptors in other areas include decreased salivation, secretion and bowel motility in the gastrointestinal tract and contraction of vascular and other smooth muscle, causing vasoconstriction.^{128, 129} The effect of dexmedetomidine on the sympathetic nervous system results in hypotension and bradycardia resulting in decreased cardiac output.¹²⁸⁻¹³⁰ Bradycardia may occur in 43% of cases, hypotension in 53% and hypertension in 28%.^{130, 131} Yapici et al. reported that hypotension and bradycardia occurred in the dexmedetomidine group and that this was managed with fluid administration or by reducing the dexmedetomidine infusion rate.

Yapici et al. stated that “considering the pre-existing cardiac problems of these patients, we did not use bolus dosing regimens or administer an initial dose in <10 minutes. Therefore, we did not observe any hemodynamic side effects”.⁷⁰ (p97) However, it was reported that “we found significantly different heart rates between the groups at 12- and 24-hour time points, that may be due to inhibited sympathetic activity causing a decrease in heart rate”.⁷⁰ (p97) Also, Yapici et al. briefly reported that hypotension was identified and that it was managed with fluid administration or reducing the dexmedetomidine dose rather than treating it as an adverse effect. There was no mention of an overt a priori intention to monitor and report harms, therefore it can be concluded that these known effects were not identified as drug harms relating to the intervention.

During the initial postoperative period following cardiac surgery, cardiac function is often variable as a result of large fluid shifts and inflammation.^{60, 61} This may lead to haemodynamic vulnerability and instability.^{60, 61} Postoperative cardiac patients are reliant on adequate cardiac output.^{60, 61} Cardiac output is dependent on adequate heart rate and stroke volume.⁶¹⁻⁶³ Low cardiac output may lead to low coronary perfusion and therefore impaired cardiac function.^{61, 63} This in turn may lead to tissue and cerebral hypoperfusion and multiorgan dysfunction, increasing the risk of death.^{60, 61, 63, 132} Careful consideration must be exercised when administering dexmedetomidine in this patient cohort.

All three clinical trials emphasised the benefits of the interventions under investigation with little reference to the associated harms. For all three studies harms reporting was limited. As there was a paucity of information it is difficult to ascertain if there was an absence of adverse effects or if adverse effects were not measured or reported.

When reporting and analysing harms there are standards that researchers and reviewers should adhere to.^{104, 105} These statements have been developed in order to generate balanced results and conclusions that

address both benefits and harms of interventions.^{104, 105} Benefits are often accorded greater prominence when reporting results in trials with little effort made to report harms.^{104, 105}

For RCTs, the CONSORT harms extension, highlights the necessity for clinical trials to report both benefits and harms of interventions and provides a 22-item checklist and flow diagram for reporting results.¹⁰⁴ The aim of this statement is to improve the quality of reporting of drug effectiveness and harms. Originally, there was only one checklist item that addressed the reporting of safety. However, in 2003 there was considerable evidence suggesting that harms related data reported in RCTs needed improving, with a working group established to address the deficit.¹⁰⁴ From this, ten new recommendations were added related to reporting harms that were then developed into the 22-item checklist. Within this was the recommendation to use the term “harm” rather than safety as “safety” may be misused or result in misleading conclusions. “Harms” is also preferred as the term encompasses unintended side effects, adverse events, adverse effects and drug reactions.¹⁰⁴ For systematic reviews and meta-analyses, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement is available.¹⁰⁵ This statement provides an evidence-based, minimum set of items for harms reporting reviews that evaluate RCTs.¹⁰⁵

A previously conducted systematic review was identified⁷⁵ from the preliminary search which was similar in part to this review. However, there were some significant differences and a number of limitations. Firstly, recommendations made by PRISMA, extension for harms reporting in systematic reviews was not systematically followed. Mu et al.⁷⁵ assessed both effectiveness and harms however events considered harmful to this patient cohort were not described. The adverse effects were not assessed using a structured tool nor critically appraised in a systematic way. Additionally, the search strategy conducted by Mu et al.⁷⁵ was a limited search in five databases for published RCTs with a limited timeframe from 1937 to 2013 with no examination of the unpublished or grey literature. Limited details relating to search terms were provided. It remains unclear if Mu et al.⁷⁵ restricted their sample to postoperative cardiac surgical patients treated in the ICU. With regards to the comparators, Mu et al.⁷⁵ noted that “studies with comparisons of pharmacological agents for sedation or pain were excluded”^{75(p195)} which differs to the current systematic review. Overall, Mu et al.⁷⁵ found inconclusive evidence to support the treatment of delirium using pharmacological agents, a finding that aligned with the findings of the current review. Additional existing review protocols and completed systematic reviews on the effectiveness of pharmacological agents used for the treatment of delirium identified from the search focused on prevention rather than treatment and therefore, could not be aligned with this review.^{76-79, 80} The findings from all the excluded studies, except one¹⁰⁹ produced similar results. These studies were observational studies and therefore excluded from this review as the preference was for experimental studies.^{3, 111} One cohort study that was identified as a precursor to an included RCT⁷¹ found ondansetron to

be effective in the treatment of hyperactive delirium after cardiac surgery.¹⁰⁹ This finding differed from this review's findings however due to quality concerns, lack of detail in reporting and no reporting related to drug harms caution is advised.¹⁰⁹

Conclusion

There is currently insufficient evidence to confirm or refute the effectiveness of morphine compared with haloperidol, ondansetron compared with haloperidol or dexmedetomidine compared with midazolam for reducing the duration or severity of hyperactive delirium in the postoperative cardiac surgical patient treated in the ICU after cardiac surgery. The available evidence indicates there are no clinically significant differences in the outcomes measured. Harms reporting was superficial and insufficiently addressed for all three studies. This review found the included studies emphasised the effectiveness of the trialed intervention with no examination of the known and significant harms that may occur from the administration of these pharmacological agents to this patient cohort.

Strengths and Limitations of the review

The main strength of the review was that it was conducted systematically according to validated procedures using an a priori protocol.⁹⁹ We also examined the harms reporting of the included studies which although important, is seldom reported in reviews of effectiveness. In addition, the search strategy of this review was extensive, examining both published, unpublished and grey literature with an unlimited timeframe but limited to English language only. The main limitations of this review pertain primarily to a lack in the number of quality studies on the treatment of hyperactive delirium identified in patients after cardiac surgery. Another limitation of this review was the exclusion of other subtypes of delirium such as subsyndromal, mixed or hypoactive delirium.

Implications for practice

Summary of Findings (SoF) tables using the GRADE approach to rate the quality of the evidence were created and are presented in Tables 10-12. Utilising GRADE provided a transparent and structured process where the evidence was rated on the following: absolute risk for the treatment, ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias.¹⁰⁷ The outcomes reported in the SoF include: mortality, duration, severity or presence of delirium, harms related to pharmacological interventions and were found to be of low quality. There is insufficient evidence to support the use of morphine, ondansetron or dexmedetomidine as effective pharmacological agents in treating hyperactive delirium. There is insufficient information to inform the development of practice guidelines. Until better quality evidence is available, practices relating to the effective management of hyperactive delirium after cardiac surgery will continue to be informed by clinical judgment and clinician discretion within local current policies and guidelines. It is imperative that clinicians remain vigilant to the known indications, contraindications and associated harms of the pharmacological agents that are being administered and to understand the implications of such drugs on cardiac performance in the initial postoperative recovery phase after cardiac surgery. Therefore, it is vital that the potential harms associated with any pharmacological agent are carefully considered in the context of the patient condition and setting

Implications for research

Future large-scale, high-quality, multi-center RCTs are required in this area, in which reliable and valid outcome measures are consistently applied. Future trials need to accord harms the same attention as treatment benefits and follow the recommendations as defined by the CONSORT harms extension. Future systematic reviews should also consider following the recommendations for harms reporting as defined by the PRISMA extension for harms reporting in systematic reviews. In lieu of high-quality RCTs, future reviews could consider the inclusion of high-quality, observational studies. This would provide clinicians with balanced reports on both the benefits and harms of drug interventions so that informed decisions can be made based on unbiased evidence.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this project.

Summary of Findings

Table 10: Morphine vs Haloperidol

Effectiveness and harms of pharmacological interventions in the treatment of delirium after cardiac surgery			
<p>Bibliography: Leigh V, Stern C, Elliott R, Tufanaru C. Effectiveness and harms of pharmacological interventions in the treatment of delirium in adults in intensive care units post cardiac surgery: a systematic review protocol. JBI Database System Rev Implement Rep. 2019; (in press)</p>			
<p>Patient or population: Adults, treatment of delirium after cardiac surgery Setting: Cardiothoracic Intensive Care Unit Intervention: Morphine Comparison: Haloperidol</p>			
Outcomes	Impact	N _e of participants (studies)	Certainty of the evidence (GRADE)
Mortality assessed with: number of deaths that occurred in each study group	No significant difference in hospital mortality reported between groups (p=0.610)	53 (1 RCT)	⊕○○○ VERY LOW ^{a,b,d}
Total duration of delirium assessed with: Confusion Assessment Method for Intensive Care Unit (CAM-ICU)	No significant difference in duration of delirium between groups (p=0.607)	53 (1 RCT)	⊕○○○ VERY LOW ^{a,b,e}
Severity of the delirium assessed with: Richmond Agitation Sedation Scale (RASS)	Severity of delirium was reduced in both groups in conjunction with decreased RASS scores, decreased drug dose over an increased number of days. No statistical data reported.	53 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c,e}
Harms related to pharmacological interventions Assessed with: observation	No adverse effects related to the pharmacological interventions were observed with no further details provided. No statistical data was reported.	53 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c,d,e,f}
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval</p>			
<p>GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>			

Explanations

- Concerns related to true randomisation, performance bias and allocation concealment
- Concerns with small sample size. Sample size calculations to establish statistical power not reported
- Confidence intervals, odds ratio, absolute risk or relative risks were not provided
- Concerns related to Intention-to-Treat (ITT), no follow-up, attrition bias, missing outcome data
- Concerns related to reliability and validity. No reporting on the number of raters, training of the raters, the intra-rater reliability or the inter-rater reliability within the study
- Harms not predefined. Concerns related to the process of collecting harms data with no statistical data reported.

Table 11: Ondansetron vs Haloperidol

Effectiveness and harms of pharmacological interventions in the treatment of delirium after cardiac surgery			
Bibliography: Leigh V, Stern C, Elliott R, Tufanaru C. Effectiveness and harms of pharmacological interventions in the treatment of delirium in adults in intensive care units post cardiac surgery: a systematic review protocol. JBI Database System Rev Implement Rep. 2019; (in press)			
Patient or population: Adults, treatment of delirium after cardiac surgery			
Setting: Cardiothoracic Intensive Care Unit			
Intervention: Ondansetron			
Comparison: Haloperidol			
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Severity of delirium assessed with: 4-point scale developed by Bayinder et al. 2000	Statistically significant improvement in test score rating after administration of both ondansetron and haloperidol (p=0.01) but no significant difference between the intervention and the comparator (no statistical data reported).	80 (1 RCT)	⊕○○○ VERY LOW a,b,c,e
Frequency in the use of physical restraints assessed with: number of patients requiring physical restraints	Use of restraints reported in both groups. Ondansetron (n=7) vs haloperidol (n=6)	80 (1 RCT)	⊕○○○ VERY LOW .b,c
Harms related to pharmacological interventions	Reported that ondansetron was safer with milder side effects compared with haloperidol. No reporting on what side effects or adverse effects were noted in either groups. No statistical data reported. No further details were provided.	80 (1 RCT)	⊕○○○ VERY LOW c,d,e,f
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval			
GRADE Working Group grades of evidence			
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect			
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different			
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect			
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect			

Explanations

- a. Concerns related to true randomisation, performance bias and allocation concealment
- b. Concerns with small sample size. Sample size calculations to establish statistical power not reported
- c. Confidence intervals, odds ratio, absolute risk or relative risks were not provided
- d. Concerns related to Intention-to-Treat (ITT), no follow-up, attrition bias, missing outcome data
- e. Concerns related to reliability and validity. No reporting on the number of raters, training of the raters, the intra-rater reliability or the inter-rater reliability within the study
- f. Harms not predefined. Concerns related to the process of collecting harms data with no statistical data reported.

Table 12: Dexmedetomidine vs Midazolam

Effectiveness and harms of pharmacological interventions in the treatment of delirium after cardiac surgery			
Bibliography: Leigh V, Stern C, Elliott R, Tufanaru C. Effectiveness and harms of pharmacological interventions in the treatment of delirium in adults in intensive care units post cardiac surgery: a systematic review protocol. JBI Database System Rev Implement Rep. 2019; (in press)			
Patient or population: Adults, treatment of delirium after cardiac surgery			
Setting: Cardiothoracic Intensive Care Unit			
Intervention: Dexmedetomidine			
Comparison: Midazolam			
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Severity of the delirium assessed with: RASS	Reported that dexmedetomidine showed a statistically significant difference in RASS scores at 48 and 60 hours (p=0.0003 and p<0.0001, respectively).	71 (1 RCT)	⊕○○○ VERY LOW a,b,c.
Harms related to pharmacological interventions	Reported that dexmedetomidine showed a statistically significant difference in heart rates between the groups at 12 and 24 hours (p=0.0017 and p<0.0001, respectively). Hypotension was reported with no data provided.	71 (1 RCT)	⊕○○○ VERY LOW c,d,e
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval			
GRADE Working Group grades of evidence			
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect			
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different			
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect			
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect			

Explanations

- a. Concerns related to true randomisation, performance bias and allocation concealment
- b. Concerns with small sample size. Sample size calculations to establish statistical power not reported.
- c. Confidence intervals, odds ratio, absolute risk or relative risks were not provided
- d. Concerns related to Intention-to-Treat (ITT), no follow-up, attrition bias, missing outcome data
- e. Harms not predefined. Concerns related to the process of collecting harms data with no statistical data reported.

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APPENDICES

Appendix I: Search strategy

NCBI PubMed. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	Delirium[mh] OR delirium*[tw] OR delirious[tw] OR confusion[mh] OR confusion[tw] OR confused state*[tw] OR ICU syndrome[tw] OR intensive care syndrome[tw] OR psychoses[tw] OR psychosis[tw] OR emergence agitation[tw] OR postanesthetic excitement[tw]	94693
#2	Cardiac surgical procedures[mh] OR cardiac surgical procedure*[tw] OR heart[mh] OR heart surg*[tw] OR cardiac surgery[mh] OR cardiac surg*[tw] OR cardiovascular surg*[tw] OR coronary artery bypass[tw] OR cardiac artery bypass[tw] OR aortic valve rep*[tw] OR CABG[tw] OR AVR[tw] OR mitral valve rep*[tw] OR MVR[tw] OR heart valve surg*[tw] OR transcatheter aortic valve implantation [tw] OR TAVI[tw]	680788
#3	Postoperative period[mh] OR postoperative period*[tw] OR post operative period[tw] OR postop[tw] OR cardiac care[tw] OR intensive care unit[mh] OR intensive care[tw] OR ICU[tw] OR critical care[tw] OR critically ill[tw] OR coronary care[tw]	303777
#4	Pharmacology[mh] OR pharmacol*[tw] OR pharmacology[sh] OR medication therapy management[mh] OR drug therapy[mh] OR drug therap*[tw] OR drug management[tw] OR drug treatment[tw] OR adrenergic alpha-2 [tw] OR dexmedetomidine[tw] OR precedex[tw] OR imidazolines[tw] OR imidazolines[mh] OR imidazoline*[tw] OR clonidine[tw] OR benzodiazepinones[mh] OR benzodiazepines[tw] OR midazolam[tw] OR diazepam[tw] OR valium[tw] OR haloperidol[tw] OR serenace[tw] OR seroquel[tw] OR central nervous system depressants[mh] OR hypnotics and sedatives[tw] OR central nervous system depressants[tw] OR CNS depressant*[tw] OR propofol[tw] OR sedat*[tw] OR antipsychotics[mh] OR antipsychotics[tw] OR antipsych*[tw] OR quetiapine[tw] OR	7216320

	anticholesteremic agents[mh] OR statin*[tw] OR ondansetron[tw]	
#5	#1 AND #2 AND #3 AND #4	236
No limitations on date. Language limited to English		

EBSCO CINAHL. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	TX Delirium OR TX delirious OR TX "confused state" OR TX agitation OR TX confusion OR TX ICU syndrome OR TX intensive care syndrome OR TX ICU psychosis OR TX intensive care psychosis OR TX psychosis OR TX psychoses OR TX psychos* OR TX emergence agitation OR TX postanesthetic excitement	550057
#2	TX Cardiac surgical procedures OR MH "Heart Valve Diseases+/SU" OR MH heart surgery OR TX heart surg* OR MH cardiac surgery OR TX cardiac surg* OR TX cardiovascular surgery OR TX coronary artery bypass OR TX cardiac artery bypass OR TX aortic valve rep* OR TX CABG OR TX AVR OR TX mitral valve rep* OR TX MVR OR TX heart valve surg* OR TX transcatheter aortic valve implantation OR TX TAVI	165986
#3	MH Postoperative period OR TX postoperative period OR TX post operative period OR TX postoperative period* OR TX postop* OR TX cardiac care OR MH intensive care OR TX intensive care OR TX ICU OR TX critical care OR TX critically ill OR TX coronary care	620035
#4	TX Pharmacology OR TX pharma* OR TX medication therapy management OR TX drug therapy OR TX drug therap* OR TX drug management OR TX drug treatment OR TX adrenergic alpha-2 OR TX dexmedetomidine OR TX precedex OR TX imidazolines OR TX imidazoli* OR TX clonidine OR TX benzodiazepines OR TX benzodiaz* OR TX midazolam OR TX midaz* OR TX diazepam OR TX diaz* OR TX valium OR TX haloperidol OR TX serenace OR TX seroquel OR TX central nervous system depressants OR	1024958

	TX hypnotics and sedat*OR TX propofol OR TX sedat* OR TX antipsychotics OR TX antipsych* OR TX quetiapine OR TX anticholesteremic agents OR TX hydroxymethylglutaryl-CoA Reductase inhibitors OR TX statin* OR TX ondansetron OR TX zofran	
954#5	#1 AND #2 AND #3 AND #4	4497
No limitations on date. Language limited to English		

Elsevier Embase. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	Delirium:ti,ab OR delirum*/de OR delirious:ti,ab OR confusion:ti,ab OR confusion/de OR "confused state":ti,ab OR "cognitive defect*/de OR "postoperative cognitive dysfunction":ti,ab OR agitation:ti,ab OR "ICU syndrome":ti,ab OR "intensive care syndrome":ti,ab OR "ICU psychosis"/de OR "ICU psychosis":ti,ab OR "intensive care psychosis":ti,ab OR psychosis:ti,ab OR psychoses:ti,ab OR psychos*:ti,ab OR "emergence agitation":ti,ab OR "postanesthetic excitement":ti,ab	432612
#2	"heart surg*":ti,ab OR "cardiac surg*":ti,ab OR "cardiovascular surgery"/de OR "cardiovascular surg*/de OR "coronary artery bypass":ti,ab OR "cardiac artery bypass":ti,ab OR "aortic valve rep*":ti,ab OR CABG:ti,ab OR AVR:ti,ab OR "mitral valve rep*":ti,ab OR MVR:ti,ab OR "heart valve surg*":ti,ab OR "transcatheter aortic valve implantation":ti,ab OR TAVI:ti,ab	263549
#3	"Postoperative period"/de OR "postoperative period":ti,ab OR "post operative period":ti,ab OR "postoperative period*":ti,ab OR postop*:ti,ab OR "cardiac care":ti,ab OR "intensive care unit"/de OR "intensive care":ti,ab OR ICU:ti,ab OR "critical care":ti,ab OR "critically ill":ti,ab OR "coronary care":ti,ab	1018324
#4	Pharmacology/de OR pharmacol*:ti,ab OR "medication therapy management"/de OR "drug therapy"/de OR "drug therap*":ti,ab OR "drug management":ti,ab OR "drug treatment":ti,ab OR "adrenergic alpha-2":ti,ab	1452244

	OR dexmedetomidine:ti,ab OR precedex:ti,ab OR imidazolines:ti,ab OR imidazolines/de OR imidazolines:ti,ab OR imidazoline*:ti,ab OR clonidine:ti,ab OR "benzodiazepine derivative"/de OR benzodiazepines:ti,ab OR midazolam:ti,ab OR diazepam:ti,ab OR valium:ti,ab OR haloperidol:ti,ab OR serenace:ti,ab OR seroquel:ti,ab OR "central nervous system depressants"/de OR "central nervous system depressants":ti,ab OR "hypnotics and sedatives"/de OR "hypnotics and sedatives":ti,ab OR propofol:ti,ab OR sedat*:ti,ab OR antipsychotics/de OR antipsychotics:ti,ab OR antipsych*:ti,ab OR quetiapine:ti,ab OR "anticholesteremic agents"/de OR "anticholesteremic agents":ti,ab OR statin*:ti,ab OR ondansetron:ti,ab	
#5	#1 AND #2 AND #3 AND #4	380
No limitations on date. Language limited to English		

Wiley Online Library Cochrane Central Register of Controlled Trials. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR confused state* OR ICU syndrome OR intensive care syndrome OR ICU psychosis OR intensive care psychosis OR psychoses OR psychos* OR emergence agitation OR postanesthetic excitement	27987
#2	Cardiac surgical procedures OR cardiac surgical procedure* OR heart surgery OR heart surg* OR cardiac surgery OR cardiac surg* OR cardiovascular surgery OR coronary artery bypass OR cardiac artery bypass OR aortic valve rep* OR CABG OR AVR OR mitral valve rep* OR MVR OR heart valve surg* OR transcatheter aortic valve implantation OR TAVI	38969
#3	Postoperative period OR post operative period OR postoperative period* OR postop* OR cardiac care OR intensive care unit OR intensive care OR ICU OR critical care OR critically ill OR coronary care	143508

#4	Pharmacology OR pharma* OR pharmacol* OR medication therapy management OR drug therapy OR drug therap* OR drug management OR drug treatment OR adrenergic alpha-2 OR dexmedetomidine OR precedex OR imidazolines OR imidazolines OR imidazoline* OR clonidine OR benzodiazepinones OR benzodiazepines OR midazolam OR diazepam OR valium OR haloperidol OR serenace OR seroquel OR central nervous system depressants OR hypnotics and sedatives OR propofol OR sedat* OR antipsychotics OR antipsych* OR quetiapine OR anticholesteremic agents OR statin* OR ondansetron	504619
#5	#1 AND #2 AND #3 AND #4	1101
No limitations on date. Language limited to English		

Elsevier Scopus. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR “confused state*” OR ICU syndrome OR “intensive care syndrome” OR ICU psychosis OR “intensive care psychosis” OR psychoses OR psychos* OR “emergence agitation” OR “postanesthetic excitement”	22064
#2	“Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery” OR “Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery”	594353
#3	“Postoperative period” OR “post operative period” OR “postoperative period*” OR postop* OR “cardiac care” OR “intensive care unit” OR “intensive care” OR ICU OR “critical care” OR “critically ill” OR “coronary care”	2683587

#4	Pharmacology OR pharma* OR pharmacol* OR “medication therapy management” OR “drug therapy” OR “drug therap*” OR “drug management” OR “drug treatment” OR “adrenergic alpha-2” OR dexmedetomidine OR precedex OR imidazolines OR imidazoline* OR clonidine OR benzodiazepinones OR benzodiazepines OR midazolam OR diazepam OR valium OR haloperidol OR serenace OR seroquel OR “central nervous system depressants” OR “hypnotics and sedatives” OR propofol OR sedat* OR antipsychotics OR antipsych* OR quetiapine OR “anticholesteremic agents” OR statin* OR ondansetron	7999559
#5	#1 AND #2 AND #3 AND #4	1705
No limitations on date. Language limited to English		

Clarivate Analytics Web of Science. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR “confused state*” OR ICU syndrome OR “intensive care syndrome” OR ICU psychosis OR “intensive care psychosis” OR psychoses OR psychos* OR “emergence agitation” OR “postanesthetic excitement”	243209
#2	“Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery” OR “Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery”	68144
#3	“Postoperative period” OR “post operative period” OR “postoperative period*” OR postop* OR “cardiac care” OR “intensive care unit” OR “intensive care” OR ICU OR “critical care” OR “critically ill” OR “coronary care”	574681
#4	Pharmacology OR pharma* OR pharmacol* OR “medication therapy management” OR “drug therapy” OR “drug therap*” OR “drug management”	1063183

	OR "drug treatment" OR "adrenergic alpha-2" OR dexmedetomidine OR precedex OR imidazolines OR imidazoline* OR clonidine OR benzodiazepinones OR benzodiazepines OR midazolam OR diazepam OR valium OR haloperidol OR serenace OR seroquel OR "central nervous system depressants" OR "hypnotics and sedatives" OR propofol OR sedat* OR antipsychotics OR antipsych* OR quetiapine OR "anticholesteremic agents" OR statin* OR ondansetron	
#5	#1 AND #2 AND #3 AND #4	342
No limitations on date. Language limited to English		

Epistemonikos Foundation EPISTEMOIKOS. Last search conducted on 18 November 2018.

Search	Query	Records retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR "confused state*" OR ICU syndrome OR "intensive care syndrome" OR ICU psychosis OR "intensive care psychosis" OR psychoses OR psychos* OR "emergence agitation" OR "postanesthetic excitement"	10
#2	"Cardiac surgical procedures" OR "cardiac surgical procedure*" OR "heart surgery" OR "heart surg*" OR "cardiac surgery" OR "cardiac surg*" OR "cardiovascular surgery" OR "Cardiac surgical procedures" OR "cardiac surgical procedure*" OR "heart surgery" OR "heart surg*" OR "cardiac surgery" OR "cardiac surg*" OR "cardiovascular surgery"	1089
#3	"Postoperative period" OR "post operative period" OR "postoperative period*" OR postop* OR "cardiac care" OR "intensive care unit" OR "intensive care" OR ICU OR "critical care" OR "critically ill" OR "coronary care"	450
#4	Pharmacology OR pharma* OR pharmacol* OR "medication therapy management" OR "drug therapy" OR "drug therap*" OR "drug management" OR "drug treatment" OR "adrenergic alpha-2" OR dexmedetomidine OR precedex OR imidazolines OR imidazoline* OR clonidine OR	37010

	benzodiazepinones OR benzodiazepines OR midazolam OR diazepam OR valium OR haloperidol OR serenace OR seroquel OR “central nervous system depressants” OR “hypnotics and sedatives” OR propofol OR sedat* OR antipsychotics OR antipsych* OR quetiapine OR “anticholesteremic agents” OR statin* OR ondansetron	
#5	#1 AND #2 AND #3 AND #4	23
No limitations on date. Language limited to English		

A hand search for primary studies published in relevant journals (2012 - 2018)

Australian Critical Care

Last search conducted on 08 September 2018.

Search Strategy	Records Retrieved
delirium AND postoperative	107
Limitations: 2012 to 2018	

Journal of Cardiothoracic Surgery

Last search conducted on 08 September 2018.

Search Strategy	Records Retrieved
delirium AND postoperative AND cardiac surgery	433
Limitations: 2012 to 2018	

American Journal of Respiratory and Critical Care Medicine

Last search conducted on 08 September 2018.

Search Strategy	Records Retrieved
delirium AND postoperative AND cardiac surgery	34
Limitations: 2012 to 2018	

Intensive Care Medicine

Last search conducted on 08 September 2018.

Search Strategy	Records Retrieved
delirium AND postoperative AND cardiac surgery	10
Limitations: 2012 to 2018	

Critical Care Medicine

Last search conducted on 08 September 2018.

Search Strategy	Records Retrieved
delirium AND postoperative AND cardiac surgery	4
Limitations: 2012 to 2018	

The search for unpublished studies in relevant websites

Australian New Zealand Clinical Trials Registry

Last search conducted on 08 September 2018.

Query	Search	Records Retrieved
#1	Delirium OR delirium* OR delirious OR confusion	182
No limitations on date. Language limited to English		

ClinicalTrials.gov

Last search conducted on 08 September 2018.

Query	Search	Records Retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR “confused state*” OR ICU syndrome OR “intensive care syndrome” OR ICU psychosis OR “intensive care psychosis” OR psychoses OR psychos* OR “emergence agitation” OR “postanesthetic excitement”	22170
#2	“Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery” OR “Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery”	2867
#3	#1 AND #2	160
No limitations on date. Language limited to English		

Clinical Trials in New Zealand

Last search conducted on 08 September 2018.

Query	Search	Records Retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR “confused state*” OR ICU syndrome OR “intensive care syndrome” OR ICU psychosis OR “intensive care psychosis” OR psychoses OR psychos* OR “emergence agitation” OR “postanesthetic excitement”	260
#2	“Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR “cardiac surgery” OR “cardiac surg*” OR “cardiovascular surgery” OR “Cardiac surgical procedures” OR “cardiac surgical procedure*” OR “heart surgery” OR “heart surg*” OR	1034

	"cardiac surgery" OR "cardiac surg*" OR "cardiovascular surgery"	
No limitations on date. Language limited to English		

ProQuest Dissertation and Theses

Last search conducted on 08 September 2018.

Query	Search	Records Retrieved
#1	Delirium OR delirium* OR delirious OR confusion OR "confused state*" OR ICU syndrome OR "intensive care syndrome" OR ICU psychosis OR "intensive care psychosis" OR psychoses OR psychos* OR "emergence agitation" OR "postanesthetic excitement"	30056

Appendix II: Studies excluded on full text

Al Tmimi L, Van de Velde M, Herijgers P, Meyns B, Meyfroidt G, Milisen K, et al. Xenon for the prevention of postoperative delirium in cardiac surgery: study protocol for a randomized controlled clinical trial. *Trials* 2015;16(449):2-9.

Reason for exclusion: Ineligible intervention. This is a study protocol for a randomized controlled trial (RCT) related to intraoperative use of xenon for the prevention of delirium.

Allen J, Alexander E. Prevention, recognition, and management of delirium in the intensive care unit. *AACN Adv Crit Care* 2012;23(1):5-11.

Reason for exclusion: Not original research. Ineligible population. This is a review paper that identifies the risks of using haloperidol. Not a primary study. Not postoperative cardiac surgical patients.

Al-Qadheeb N, Skrobik Y, Schumaker G, Pacheco M, Roberts R, Ruthazer R, et al. Preventing ICU subsyndromal delirium conversion to delirium with low-dose iv haloperidol: a double-blind, placebo-controlled pilot study. *Crit Care Med* 2016;44(3):583-91.

Reason for exclusion: Ineligible population. Pilot study re: haloperidol use preventing subsyndromal delirium in critically ill patients. Exempt population: post cardiac surgical patients.

American Association of Critical Care Nurses (AACN). Delirium Assessment and Management. [Internet]. 2012 [cited 2017 December 12]. Available from <http://ccn.aacnjournals.org/content/32/1/79.full>

Reason for exclusion: Not original research. This is a practice guideline written by the AACN on delirium management. Not related to pharmacological treatment of postop cardiac delirium. Not a primary study.

Andrade RGA. The role of ketamine in preventing cognitive dysfunctions in postoperative period of cardiac surgery. [Internet]. NCT02782429. 2016. [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02782429>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Currently in progress. No reporting of results available yet. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Andrejaitiene J. Delirium after cardiac surgery in early postoperative period: Clinical outcome. *Intensive Care Med* 2011;37:S62.

Reason for exclusion: Not original research. This is a supplementary paper on delirium as a postop complication in cardiac patients. Not related to the treatment of delirium.

Anger KE, Szumita PM, Baroletti SA, Labreche MJ, Fanikos J. Evaluation of dexmedetomidine versus propofol-based sedation therapy in mechanically ventilated cardiac surgery patients at a tertiary academic medical center. *Crit Pathw Cardiol* 2010;9(4):221-6.

Reason for exclusion: Ineligible intervention. Prospective study involving the use of dexmedetomidine vs propofol for sedation of cardiac surgical patients. Not related to the treatment of delirium.

Arora RC, Djaiani G, Rudolph JL. Prediction, prevention and management of delirium in the critically ill cardiac patient. [Internet]. NCT02206880. 2014. [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT02206880>

Reason for exclusion: Ineligible intervention. This is a clinical trial based on prediction and incidence of delirium in the postop cardiac patient. Not related to the pharmacological treatment of postop cardiac surgery delirium. Report paper is available.

Arumugam S, El-Menyar A, Al-Hassani A, Strandvik G, Asim M, Mekkodithal A, et al. Delirium in the intensive care unit. *J Emerg Trauma Shock* 2017;10(1):37–46.

Reason for exclusion: Not original research. Review paper related to delirium in the intensive care unit (ICU) patient.

Asghar A, Siddiqui KM, Ahsan K, Chughtai S. Postoperative delirium after cardiac surgery; Incidence, management and prevention. *Anaesth Pain Intens Care* 2017;21(1):109-11.

Reason for exclusion: Not original research. Special review paper related to delirium in the postop cardiac patient. Not a primary study related to treatment of delirium. No new primary studies mentioned.

Azeem TMA, Yosif NE, Alansary AM, Esmat IM, Mohamed AK. Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blinded clinical trial. [Saudi J Anaesth](#). 2018;12(2):190-197

Reason for exclusion: Ineligible intervention. This randomized controlled trial looks at the use of dexmedetomidine to prevent delirium in postop cardiac patients. Not related to pharmacological treatment of postop cardiac delirium.

Baroncelli F, Barile L, D'Agrosa L, Jain A, Lombrano MR, Marini E, Forfori F, Martinelli G, Meraglia A. Adherence to the local guidelines for the management of delirium in a cardiothoracic intensive care unit: a clinical audit. *Appl Cardiopulm Pathophysiol* 2014;18(P39):102-103

Reason for exclusion: Ineligible outcome. Observational study re: study of compliance to nursing staff monitoring and managing delirium as per APA guideline. Not related to treatment of delirium.

Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BRH, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41(1):263-306.

Reason for exclusion: Not original research. Practice guideline re: delirium management. Not related to pharmacological treatment of postop cardiac delirium. Not a primary study.

Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database of Systematic Reviews* [Internet]. 2011;(9) [cited 2018 November 18] Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008012.pub3/abstract>

Reason for exclusion: Not original research. Systematic review re: depression and cardiovascular disease.

Bayindir O, Akpınar B, Can E, Guden M, Sonmez B, Demiroglu C. Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. *Cardiothorac Vasc Anesth*. 2000;14.

Reason for exclusion: Higher level study design located. This is a prospective cohort study on the use of ondansetron for the treatment of delirium post cardiac surgery. Not an RCT.

Bily B, Artemiou P, Sabol F, Bilecova-Rabajdova M, Kolarcik P, Torok P. The role of dexmedetomidine in the prevention of postoperative delirium in cardiac surgery patients. *Cardiology Letters* 2015; 24(6):435-44.
Reason for exclusion: Ineligible intervention. This is an observational prevention study that looks at the use of dexmedetomidine to prevent delirium in postop cardiac patients. Not related to pharmacological treatment of postop cardiac delirium.

Bledowski J, Trutia A. A review of pharmacologic management and prevention strategies for delirium in the intensive care unit. *Psychosomatics* 2012;53(3):203-11.

Reason for exclusion: Not original research. Ineligible population. A systematic review on the management of delirium in the ICU. Not inclusive of cardiac surgical patients admitted into the ICU.

Bokesch PM. A phase III, randomized, double-blind, placebo-controlled, two-arm parallel, multicenter study evaluating the efficacy and safety of dexmedetomidine in the prevention of postoperative delirium in subjects with CBP. [Internet]. NCT00464763. 2007. [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT00464763>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Withdrawn due to the incidence of post-operative delirium observed from interim blinded data in DEX-06-09 was significantly lower than the current literature in this population.

Breu A, Stransky M, Metterlein T, Werner T, Trabold B. Subsyndromal delirium after cardiac surgery. *Scand Cardiovasc J* 2015;49(4):207-12.

Reason for exclusion: Ineligible population. Prospective study looking at the incidence of subsyndromal delirium after cardiac surgery. Not related to treatment of hyperactive delirium.

Brooks P, Spillane JJ, Dick K, Stuart-Shor E. Developing a strategy to identify and treat older patients with postoperative delirium. *AORN J* 2014;99(2):256-76.

Reason for exclusion: Ineligible population. This is an improvement project. Not related to postop cardiac patients. Not related to pharmacological intervention for the treatment of postop delirium.

Brown KE, Mirrakhimov AE, Yeddula K, Kwatra MM. Propofol and the risk of delirium: Exploring the anticholinergic properties of propofol. *Med Hypotheses* 2013;81(4):536-9.

Reason for exclusion: Not original research. Review paper on the risk of using propofol with the development of delirium. Not related to treatment of delirium in the postop cardiac patient.

Brown CH. Delirium in the cardiac surgical ICU. *Curr Opin Anaesthesiol* 2014;27(2):117-22.

Reason for exclusion: Not original research. This is a review paper on delirium in the cardiac surgical ICU.

Not a primary study.

Brown CH, Neufeld KJ, Needham DM. Delirium, steroids, and cardiac surgery. *Anaesth Analg* 2014;119(5):1011-3.

Reason for exclusion: Not original research. Not a primary study. This is an expert review paper. Not related to pharmacological intervention for the treatment of postop delirium.

Brown, CH. An intervention to reduce delirium after cardiac surgery [Internet]. NCT02587039; 2014 [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/results?cond=An+intervention+to+reduce+delirium+after+cardiac+surgery.+NCT02587039>.

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial involving ischemic preconditioning whereby exposing the patient to brief ischemic periods to prevent development of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Brown CHt, Laflam A, Max L, Lyman D, Neufeld KJ, Tian J, Shah AS, Whitman GJ, Hogue CW. The impact of delirium after cardiac surgical procedures on postoperative resource use. *Ann Thorac Surg*. 2016;101(5):1663-9.

Reason for exclusion: Ineligible intervention. Prospective observational study on the effect of delirium on length of stay and cost. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Bruder NJ, Velly L. Pharmacologic approach for delirium after cardiac surgery: There is no magic bullet. *Crit Care Med* 2015;43(1):256-7.

Reason for exclusion: Not original research. Interest paper. Not a primary study.

Cheng H, Li ZM, Young N, Boyd D, Atkins Z, Ji FH, Liu H. The effect of dexmedetomidine on outcomes of cardiac surgery in elderly patients. *J Cardiothorac Vasc Anesth* 2016;30(6):1502-8.

Reason for exclusion: Ineligible intervention. Retrospective study on the use of demedetomidine vs placebo and its effect on elderly cardiac surgical patients. Not related to treatment of postop delirium.

Chorney SR, Gooch ME, Oberdier MT, Keating D, Stahl RF. The safety and efficacy of dexmedetomidine for postoperative sedation in the cardiac surgery intensive care unit. *HSR Proc Intensive Care Cardiovasc Anesth* 2013;5(1):17-24.

Reason for exclusion: Ineligible intervention. Retrospective study on the use of dexmedetomidine on early extubation post cardiac surgery. Not related to treatment of postoperative delirium.

Clarke SP, McRae ME, Del Signore S, Schubert M, Styra R. Delirium in older cardiac surgery patients: directions for practice. *J Gerontol Nurs* 2010;36(11):34-45.

Reason for exclusion: Not original research. Practice guideline on risk factors, prevention and treatment of delirium. Not a primary study.

Cooke SE, Dasta J, Fish D, Hassan E, Horst HM, Kelly K, Kaiser K, Jackson CE, Rudis M, Schoenberger C, Schoonover L, Takaniski G, Teres D, Thompson K. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Am J Health Syst Pharm* 2002;59(2):150-78.

Reason for exclusion: Not original research. This is a clinical practice guideline on the management of pain and sedation in the critically ill. Not related to the treatment of post cardiac surgery delirium.

Cottrell JE, Hartung J. Developmental disability in the young and postoperative cognitive dysfunction in the elderly after anesthesia and surgery: do data justify changing clinical practice? *Mt Sinai J Med* 2012;79(1):75-94.

Reason for exclusion: Not original research. Interest paper on the effects of anesthetic on a young and old brain. Not related to the treatment of post cardiac surgery delirium.

Crippen D. Life-threatening brain failure and agitation in the intensive care unit. *Crit Care*. 2000;4(2):81-90.

Reason for exclusion: Not original research. Interest paper on the effects of alcohol and delirium on the ICU patient. Not related to the treatment of post cardiac surgery delirium.

Cropsey C, Kennedy J, Han J, Pandharipande P. Cognitive dysfunction, delirium, and stroke in cardiac surgery patients. *Semin Cardiothorac Vasc Anesth*. 2015;19(4):309-17.

Reason for exclusion: Not original research. Review paper. Not a primary study.

Crowley K, Urben L, Hacobian G, Geiger K. Valproic acid for the management of agitation and delirium in the intensive care setting. *Crit Care Med* 2018;46:430.

Reason for exclusion: Not original research. This is an abstract paper. Not a primary study. Author contacted. Paper yet to be published and was unavailable at the time of this review.

Cruz JN, Tomasi CD, Alves SC, Macedo RC, Giombelli V, Cruz JG, Dal-Pizzol F, Ritter C. The incidence of delirium in patients pre-treated with statins who remain in an intensive care unit after cardiac surgery. *Rev Bras Ter Intensiva*. 2012;24(1):52-7.

Reason for exclusion: Ineligible intervention. This was a prospective, observational, cohort prevention study. Not related to the treatment of post cardiac surgery delirium.

Dale CR, Bryson CL, Fan VS, Maynard C, Yanez ND, Treggiari MM. A greater analgesia, sedation, delirium order set quality score is associated with a decreased duration of mechanical ventilation in cardiovascular surgery patients. *Crit Care Med* 2013;41(11):2610-7.

Reason for exclusion: Ineligible intervention. Retrospective study on the quality order set and quality score for pain, sedation and delirium in the post cardiac surgery patient. Not related to delirium treatment.

Das S, Forrest K, Howell S. General anesthesia in elderly patients with cardiovascular disorders: choice of anesthetic agent. *Drugs Aging* 2010;27(4):265-82.

Reason for exclusion: Ineligible intervention. This is a practice guide on the effects of anesthetic on the elderly patient undergoing surgery. Not related to delirium treatment.

Dattilio FM, Castaldo JE. Differentiating cognitive impairment from symptoms of anxiety in postcoronary artery bypass grafting encephalopathy: A case report. *Neuropsychiatr Dis Treat* 2006;2(1):111-6.

Reason for exclusion: Ineligible intervention. This is a case report on anxiety and non-pharmacological treatment on the post-op coronary artery bypass graft patient. Not related to pharmacological treatment of delirium in the postop surgical patient.

Davidson JE, Winkelman C, G elinas C, Dermenchyan A. Pain, agitation, and delirium guidelines: nurses' involvement in development and implementation. *Crit Care Nurse* 2015;35(3):17-31.

Reason for exclusion: Not original research. This is a manuscript on the importance of nurse involvement in writing guidelines, example used pain, agitation and delirium. Not related to pharmacological treatment of delirium in the postop surgical patient.

DeForest A, Blinderman CD. Persistent delirium in chronic critical illness as a prodrome syndrome before death. *J Palliat Med* 2017;20(5):569-72.

Reason for exclusion: Higher level study design located. This is a case presentation on caring for a patient with persistent delirium before death. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Dianatkah M, Ghaeli P, Talasaz AH, Karimi A, Salehiomran A, Bina P, Jalali A, Ghaffary S, Shahmansouri N, Vejdani S. Evaluating the potential effect of melatonin on the post- cardiac surgery sleep disorder. *J Tehran Heart Cent* 2015;10(3):122-8.

Reason for exclusion: Ineligible intervention. This is an RCT, double-blinded on sleep improvement with use of melatonin commenced prior to CABG surgery. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, Katznelson R. Reducing delirium after cardiac surgery: a multifaceted approach of perioperative care. [Internet]. NCT01378741. 2011[cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/results?cond=Reducing+delirium+after+cardiac+surgery%3A+a+multifaceted+ap+proach+of+perioperative+care.+NCT01378741>.

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Not related to the treatment of postop cardiac surgery delirium. Report paper written.

Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, Katznelson R. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial [Internet]. *Anesthesiol* 2016; 124(2):362-8. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/ane.13111>

Reason for exclusion: Ineligible intervention. This is an RCT prevention trial. Not related to the treatment of postop cardiac surgery delirium. This paper relates to NCT01378741.

Ellard L, Katznelson R, Wasowicz M, Ashworth A, Carroll J, Lindsay T, Djaiani G. Type of anaesthesia and postoperative delirium after vascular surgery. *J Cardiothorac Vasc Anesth* 2014;28(3):458-61.

Reason for exclusion: Ineligible intervention. This is a retrospective study on the incidence of delirium in relation to the type of anesthetic that was used in vascular patients. Not related to treatment of delirium in the postop cardiac patient.

Elkassabany N, Muravchick S, Fleisher LA. Thinking clearly about postoperative delirium and perioperative medications: how concerned should we be? *Can J Anaesth* 2009;56(11):785-8.

Reason for exclusion: Not original research. This is an editorial. Not a primary study. Not related to treatment of delirium in the postop cardiac patient.

Ellouze M, Badrudin D, Cartier R. Statins decrease incidence of delirium after OPCAB surgery. *Can J Cardiol* 2015;31(10):S173.

Reason for exclusion: Not original research. This is a published abstract. Not a primary study. Not related to treatment of delirium in the postop cardiac patient.

Erden O, Koner O, Temur S, Menda F, Bilgen S. Effects of ondansetron on sevoflurane induced pediatric emergence agitation. *Br J Anaesth* 2012;108:ii301.

Reason for exclusion: Ineligible population. This is an RCT study re: use of ondansetron to prevent emergence delirium in the pediatric population.

Esmat IM. Dexmedetomidine versus morphine and midazolam in prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blind clinical trial. [Internet]. NCT03078946 2013 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT03078946>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. At the time of searching no report was available. Report published 09 March 2018. Not related to the pharmacological treatment of postop cardiac surgery delirium with a focus of incidence of delirium.

Evans A, Weiner M, Arora R, Chung I, Deshpande R, Varghese R, Augoustides J, Ramakrishna H. Current approach to diagnosis and treatment of delirium after cardiac surgery. *Ann Card Anaesth* 2016;19(2):328-37.

Reason for exclusion: Not original research. This is a review paper. Not a primary study. Not related to pharmacological intervention for the treatment of postop delirium.

Faught DD. Delirium: the nurse's role in prevention, diagnosis, and treatment. *Medsurg Nurs* 2014;23(5):301-5.

Reason for exclusion: Not original research. This is an interest paper related to nurse education on raising awareness on delirium management and treatment. Not a primary study related to treatment of delirium in the postop cardiac patient.

Firouzian A, Khezri HD. Can *Glycyrrhiza glabra L.* reduce delirium after coronary artery bypass graft surgery? *Forsch Komplementmed* 2014;21(6):418-9.

Reason for exclusion: Not original research. This is a review paper on perioperative use of licorice for the prevention of delirium post CABG surgery. Not related to pharmacological intervention for the treatment of postop delirium.

Flacker J, Marcantonio E. Delirium in the elderly: optimal management. *Drugs Aging* 1998;13(2):119-30.

Reason for exclusion: Not original research. This is a management guideline. Not a primary study. Not related to pharmacological intervention for the treatment of postop delirium.

Fok MC, Sepehry AA, Frisch L, Sztramko R, van der Burg BLS, Vochteloo AJH, Chan P. Do antipsychotics prevent postoperative delirium? A systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2015;30(4):333-44.

Reason for exclusion: Not original research. Ineligible population. This is a systematic review re: drugs to prevent delirium in the postop patient. Excludes postop cardiac patients.

Fong JJ, Devlin J. Can postoperative delirium be prevented pharmacologically? *Crit Care Med* 2009;37(5):1825-6.

Reason for exclusion: Not original research. Review paper. Not a primary study. Re: focus of prevention rather than treatment of delirium in the postop patient.

Ford AH, Almeida OP. Pharmacological interventions for preventing delirium in the elderly. *Maturitas* 2015;81(2):287-92.

Reason for exclusion: Not original research. Ineligible population. This is a systematic review re: drugs to prevent delirium in the postop patient. Excludes postop cardiac patients.

Ford AH, Flicker L, Passage J, Wibrow B, Anstey M, Edwards M, Almeida OP. The Healthy Heart-Mind trial: melatonin for prevention of delirium following cardiac surgery: study protocol for a randomized controlled trial. *Trials* 2016;17.

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial protocol. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Foushee J, Bush S, Furmanek D, Ohanuka E, Wright C, Kudlak J, Cass A. Postoperative delirium risk factors and outcomes in a cardiovascular intensive care unit. *Crit Care Med* 2010;38:A227.

Reason for exclusion: Not original research. This is a published abstract. Unable to find full text. Author contacted but no response. Not a primary study.

Fuentes Fernandez I, Moreno Flores A, Albacete Moreno C, Jara Rubio R. Basal cortisol relationship with the appearance of postoperative delirium. *Eur J Neurol* 2015;22:569.

Reason for exclusion: Not original research. This is a poster presentation. Unable to find full text. Not a primary study. Not related to pharmacological intervention for the treatment of postop delirium.

Fuhai., Li Z, Nguyen H, Young N, Shi P, Fleming N, Liu H. Perioperative dexmedetomidine improves outcomes of cardiac surgery. *Circ* 2013;127(15):1576-84.

Reason for exclusion: Ineligible intervention. This is a retrospective cohort prevention study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Fuhai, Li Z, Young N, Moore P, Liu H. Perioperative dexmedetomidine improves mortality in patients undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2014;28(2):267-73.

Reason for exclusion: Ineligible intervention. This is a retrospective cohort prevention study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Fukata S, Kawabata Y, Fujishiro K, Kitagawa Y, Kuroiwa K, Akiyama H, Takemura M, Ando M, Hattori H. Haloperidol prophylaxis for preventing aggravation of postoperative delirium in elderly patients: a randomized, open-label prospective trial. *Surg Today*. 2017;47(7):815-26.

Reason for exclusion: Ineligible intervention. Ineligible population. This is RCT is a prevention trial. Population group is elderly abdominal and orthopedic surgical patients. Not postoperative cardiac surgical patients. Not related to pharmacological intervention for the treatment of postop delirium.

Gamberini M, Bolliger D, Buse GAL, Burkhart CS, Grapow M, Gagneux A, Filipovic M, Seeberger MD, Pargger H, Siegemund M, Carrel T, Seiler WO, Berres M, Strebel SP, Monsch AU, Steiner LA. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery-A randomized controlled trial. *Crit Care Med* 2009;37(5):1762-8.

Reason for exclusion: Ineligible intervention. This RCT is a prevention trial. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Geng J, Qian J, Cheng H, Ji F, Liu H. The influence of perioperative dexmedetomidine on patients undergoing cardiac surgery: A meta-analysis. *Plos One* 2016;11(4).

Reason for exclusion: Not original research. This is a meta-analysis. Not a primary study. Re: focus of prevention rather than treatment of delirium in the postop patient.

Gosch M, Nicholas JA. Pharmacologic prevention of postoperative delirium. *Z Gerontol Geriatr* 2014;47(2):105-9.

Reason for exclusion: Not original research. This is a review paper on the prevention of postop cardiac surgery delirium. Not a primary study. Not related to the treatment of postop cardiac surgery delirium.

Grey R, Brohan J. Dexmedetomidine use in ICU sedation and postoperative recovery in elderly patients and post-cardiac surgery [Internet]. NCT02699801. 2016 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02699801>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Currently in progress. No reporting of results available yet. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Giffhorn H. The incidence of delirium in patients pretreated with statins who remain in an intensive care unit after cardiac surgery. *Rev Bras Ter Intensiva* 2012;24(3):312-3.

Reason for exclusion: Not original research. This is a letter to the editor. Not a primary study. Re: focus of prevention rather than treatment of delirium in the postop patient.

Groen JA, Banayan D, Gupta S, Xu S, Bhalerao S. Treatment of delirium following cardiac surgery. *J Card Surg* 2012;27(5):589-93.

Reason for exclusion: Not original research. This is a review paper. Not a primary study. Re: focus of prevention rather than treatment of delirium in the postop patient.

Gu WE. Impact of dexmedetomidine sedation on the post-operative cognition dysfunction - a multiple center, randomized, controlled, double blinded clinical trial. [Internet]. NCT02275182. 2014 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02275182>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Results have not yet been published. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Hakim S, Othman A, Naoum D. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. *Anesthesiol* 2012;116(5):987-97

Reason for exclusion: Ineligible population. This trial involved the use of risperidone for the treatment of subsyndromal delirium. Not hyperactive delirium.

Haque N, Dasgupta M, Naqvi RM. A systematic review on the efficacy of ondansetron in the prevention and treatment of post-operative delirium. *Eur Geriatr Med* 2016;7:S20-S1.

Reason for exclusion: Not original research. This is a systematic review. Not a primary study on the use of ondansetron on the treatment of postop cardiac surgery delirium.

Hartwick SS. ICU delirium: a case study. *Crit Care Nurs Q* 2003;26(3):221-4.

Reason for exclusion: Not original research. This is a case study on a patient's perspective on experiencing delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Hauffe T, Kruger B, Bettex D, Rudiger A. Shock Management for cardio-surgical intensive care unit patient: the silver days. *Card Fail Rev* 2016;2(1):56-62.

Reason for exclusion: Not original research. This is a review on the management of shock in the cardiac patient. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Hlaing M. Immediate ICU care for patients following aortic arch surgery. *Semin Cardiothorac Vasc Anesth*. 2016;20(4):333-42.

Reason for exclusion: Not original research. This is a review paper on the immediate postop cardiac surgery period. Not a primary study. Not related to the treatment of postop cardiac surgery delirium.

Hollinger A, Ledergerber K, Von Felten S, Sutter R, Rüegg S, Gantner L, Zimmermann S, Blum A, Steiner LA, Marsch S, Siegemund M. Comparison of propofol and dexmedetomidine infused overnight to treat hyperactive and mixed ICU delirium: A protocol for the Basel ProDex clinical trial. *BMJ Open* 2017;7(7).
Reason for exclusion: Not original research. This is a protocol paper for a clinical trial that is yet to be completed.

Hori D, Max L, Laflam A, Brown C, Neufeld KJ, Adachi H, Sciortino C, Conte JV, Cameron DE, Hogue CW, Jr., Mandal K. Blood pressure deviations from optimal mean arterial pressure during cardiac surgery measured with a novel monitor of cerebral blood flow and risk for perioperative delirium: a pilot study. *J Cardiothorac Vasc Anesth* 2016;30(3):606-12.
Reason for exclusion: Ineligible outcome. This is a pilot study on whether blood pressure management resulted in post cardiac surgery delirium

Hou BJ, Du Y, Yu J, Ping FM, Jin M, Gu SX, Wan L, Wang HB. Influence of different anesthesia methods on the cognitive ability and myocardial damage in cardiac surgery. *Int J Clin Exp Med* 2017;10(8):12856-61.
Reason for exclusion: Ineligible outcome. This is an RCT regarding the effect of anesthesia on cognitive function post-surgery. Not related to treatment of delirium in the postop cardiac patient.

Hsieh SJ, Fuster D, D'Alessandro DA, Leff JD, Gong MN. Feasibility and efficacy of intranasal insulin for post-operative delirium: The CNS-elders randomized controlled trial. *Am J Respir Crit Care Med* 2015;191.
Reason for exclusion: Ineligible intervention. This RCT is a prevention trial. Unable to find published results other than an abstract. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, Warltier DC, Pagel PS. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2009;23(5):651-7.
Reason for exclusion: Ineligible intervention. This RCT is a prevention trial. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Hudetz JA, Hoffmann RG, Patterson KM, Byrne AJ, Iqbal Z, Gandhi SD, Wartier DC, Pagel PS. Preoperative dispositional optimism correlates with a reduced incidence of postoperative delirium and recovery of postoperative cognitive function in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 2010;24(4):560-7.

Reason for exclusion: Ineligible intervention. This is an observational study on the influence of social structure on postop delirium in the cardiac surgical patient. No relation to pharmacological treatment of delirium in the postop cardiac patient.

Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Pagel PS. Postoperative delirium and short-term cognitive dysfunction occur more frequently in patients undergoing valve surgery with or without CABG surgery compared with CABG surgery alone. *J Cardiothorac Vasc Anesth* 2011;25(5):811-6.

Reason for exclusion: Ineligible outcome. This is a prospective study on comparing valve +/- grafts with graft surgery alone. Not related to pharmacological treatment of delirium in the postop cardiac patient.

Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Pagel PS. Remote ischemic preconditioning prevents deterioration of short-term postoperative cognitive function after cardiac surgery using cardiopulmonary bypass: results of a pilot investigation. *J Cardiothorac Vasc Anesth*. 2015;29(2):382-8.

Reason for exclusion: Ineligible intervention. This RCT is a prevention trial. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Indrambarya T. Effect of dexmedetomidine infusion on post-operative cognitive function and oxidative stress in patients undergo cardiopulmonary bypass machine facilitated elective cardiac surgery. [Internet]. NCT03054857. 2015 [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT03054857>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Trial completed. No reporting of results available yet. Not related to the pharmacological treatment of postop cardiac surgery delirium.

John M, Ely E, Halfkann D, Schoen J, Sedemund-Adib B, Klotz S, Radtke F, Stehr S, Hueppe M. Acetylcholinesterase and butyrylcholinesterase in cardiosurgical patients with postoperative delirium. Journal of intensive care [Internet]. [cited 2017 December 12] 2017; 5(1). Available from:

<http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/480/CN-01383480/frame.html>

Reason for exclusion: Ineligible outcome. This is an RCT on the measuring of acetylcholinesterase and butyrylcholinesterase levels in patients who develop postoperative delirium post cardiac surgery and if those levels were the same as patients who underwent non-cardiac surgery. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Johnson-Akeju. Minimizing icu neurological dysfunction with dexmedetomidine-induced sleep (MINDDDS): a randomized placebo-controlled trial. [Internet]. NCT02856594. [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT02856594>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Currently in progress. No reporting of results available yet. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Kadoi Y, Saito S, Kunimoto F, Goto F, Fujita N. Comparative effects of propofol versus fentanyl on cerebral oxygenation state during normothermic cardiopulmonary bypass and postoperative cognitive dysfunction.

Ann Thorac Surg 2003;75(3):840-6.

Reason for exclusion: Ineligible intervention. This is an RCT on the use of propofol vs fentanyl intraoperatively on cerebral oxygenation and long term cognitive function. Not related to treatment of delirium in the postop cardiac patient.

Kadoi Y. Pharmacological neuroprotection during cardiac surgery. Asian Cardiovasc Thorac Ann 2007;15(2):167-77.

Reason for exclusion: Ineligible intervention. This is a review on the effects of drugs administered during heart surgery on neuro function. Not related to treatment of delirium in the postop cardiac patient.

Kadoi Y. Sevoflurane anesthesia did not affect postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery. J Anesth 2007;21(3):330-5.

Reason for exclusion: Ineligible intervention. This is a retrospective study on the use of sevoflurane intraoperatively on cognitive function. Not related to the pharmacological treatment of delirium in the postop cardiac patient.

Karanovic N. The role of inflammatory and stress response in the pathogenesis of cognitive dysfunction after cardiac surgery. [Internet]. NCT02767713. 2015 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02767713>

Reason for exclusion: Ineligible outcome. This clinical trial is a prevention trial involving the measuring of CRP levels in postop cardiac patients and if there is any difference between those with/without delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Katznelson R, Djaiani G, Mitsakakis N, Lindsay TF, Tait G, Friedman Z, Wasowicz M, Beattie WS. Delirium following vascular surgery: increased incidence with preoperative beta-blocker administration. *Can J Anaesth* 2009;56(11):793-801.

Reason for exclusion: Ineligible population. This is a prospective study looking at whether preoperative beta blockers reduced the incidence of postop delirium in vascular patients. Population of interest is vascular patients, not postop cardiac patients.

Katznelson R, Djaiani G, Mistakakis N, Lindsay T, Tait G, Friedman Z, Beattie WS. Preoperative administration of statins and delirium after vascular surgery. *Anesthesiol* 2009;110(1):67-73.

Reason for exclusion: Ineligible population. Ineligible intervention. This is a prospective review on statin use preoperatively to prevent delirium in vascular surgical patients. Population of interest is vascular patients, not postop cardiac patients. This is a prevention study, not related to the pharmacological treatment of postop cardiac surgery delirium.

Katznelson R. Postoperative melatonin administration and delirium prevention in patients undergoing vascular and cardiac surgery. [Internet]. NCT01198938. 2010 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT01198938>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Not related to the pharmacological treatment of postop cardiac surgery delirium. No report found.

Katznelson R, Djaiani GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, Karski J, Mitsakakis N, Carroll J, Beattie WS. Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. *Can J Anaesth* 2009;56:S11.

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial that looks at the incidence of delirium with the administration of statins preoperatively. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Khasati N, Thompson J, Dunning J. Is haloperidol or a benzodiazepine the safest treatment for acute psychosis in the critically ill patient? *Interact Cardiovasc Thorac Surg* 2004;3(2):233-6.

Reason for exclusion: Not original research. This is a systematic review protocol on whether haloperidol is better than benzodiazepine. Not a primary study.

Kiberd M, Hall R. Does haloperidol cause delirium? *Crit Care Med* 2015;43(5):1143-4.

Reason for exclusion: Not original research. This is an editorial. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Kim KY, McCartney JR, Kaye W, Boland RJ, Niaura R. The effect of cimetidine and ranitidine on cognitive function in postoperative cardiac surgical patients. *Int J Psychiatry Med* 1996;26(3):295-307.

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial that looks at the incidence of delirium with the administration of either cimetidine or ranitidine postoperatively. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Kim D, Mahesri M, Bateman B, Huybrechts K, Inouye S, Marcantonio E, Herzig S, Ely EW, Pandharipande P, Pisani M, Avorn J. Variation in antipsychotic use in hospitalized older adults after cardiac surgery. *Pharmacoepidemiol Drug Saf* 2017;26:334-5.

Reason for exclusion: Ineligible outcome. This is a supplement article that evaluates the usage of antipsychotics prescribed for treating postop delirium, no effect on treatment.

Kim DH, Huybrechts KF, Paterno E, Marcantonio ER, Park Y, Levin R, Abdurrob A, Bateman BT. Adverse Events Associated with Antipsychotic Use in Hospitalized Older Adults After Cardiac Surgery. *J Am Geriatr Soc* 2017;65(6):1229-37.

Reason for exclusion: Higher level study design located. This is a retrospective cohort study on the prevention of postoperative delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Kroh M, Kee C, Reid L, Jones P. Dexmedetomidine in management of agitated delirium in the postoperative cardiac surgical patient. *Can J Cardiol* 2012;28(5):S424-S.

Reason for exclusion: Not original research. This is a supplementary article. Unable to find full text. No contact details available to follow up.

Kroll A, Cahoon W. Quetiapine-associated QTC prolongation in cardiac surgery patient with icu delirium. Crit Care Med 2015;43(12).

Reason for exclusion: Not original research. This is a supplementary article. Unable to find full text. No contact details available to follow up.

Kumar AK, Jayant A, Arya VK, Magoon R, Sharma R. Delirium after cardiac surgery: a pilot study from a single tertiary referral center. Ann Card Anaesth 2017;20(1):76-82.

Reason for exclusion: Ineligible outcome. This is an observational study looking at the risks of delirium post cardiac surgery.

Lahariya S, Grover S, Bagga S, Sharma A. Delirium in patients admitted to a cardiac intensive care unit with cardiac emergencies in a developing country: Incidence, prevalence, risk factor and outcome. Gen Hosp Psychiatry 2014;36(2):156-64.

Reason for exclusion: Ineligible outcome. This is a prospective primary study with the aim to assess the incidence, risk, prevalence and outcome of delirium of patients who underwent cardiac emergencies in developing countries. Not related to pharmacological treatment of delirium in the postop cardiac patient.

Laitinen H. Patients' experience of confusion in the intensive care unit following cardiac surgery. Intensive Crit Care Nurs 1996;12(2):79-83.

Reason for exclusion: Ineligible intervention. This study is a phenomenological-hermeneutic study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Lamy A. Haloperidol prophylaxis in cardiac surgery for patients at risk for delirium: a randomized placebo-controlled pilot study. [Internet]. NCT01862302. 2013 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT01862302>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Results have not yet been published. Supplementary paper available. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Lawrence KR, Nasraway SA. Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: a review of the literature. *Pharmacother* 1997;17(3):531-7.

Reason for exclusion: Not original research. Ineligible population. This is a literature review. Not a primary study. Re: looking at conduction abnormalities when administering droperidol or haloperidol in the critically ill. Not isolated to postop cardiac patients. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Leacche M, Carrier M, Bouchard D, Pellerin M, Perrault LP, Paga P, Hebert Y, Cartier R. Improving neurologic outcome in off-pump surgery: the "no touch" technique. *Heart Surg Forum*. 2003;6(3):169-75.

Reason for exclusion: Ineligible intervention. This is a retrospective study on preventing delirium using off-pump cardiopulmonary bypass. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Li X, Yang J, Nie X, Zhang Y, Li X, Li L, Wang D, Ma D. Dexmedetomidine and delirium in patients after cardiac surgery. [Internet]. NCT02267538. 2014 [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT02267538>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial looking at the use of dexmedetomidine intraoperatively on the incidence of delirium. Report obtained. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Likhvantsev V, Grebenchikov O, Shaibakova V, Levikov D, Cherpakov R. Neuroprotective effect of volatile induction and maintenance of the anesthesia (VIMA) vs. total intravenous anesthesia (TIVA) during on-pump coronary artery bypass grafting (CABG). *Eur J Anaesthesiol* 2013;30:54.

Reason for exclusion: Ineligible intervention. This RCT looks at the effects of sevoflurane on postop delirium. Not related to treatment of delirium in the postop cardiac patient.

Lin YY, He B, Chen J, Wang ZN. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? a meta-analysis. *Crit Care* 2012;16(5):R169.

Reason for exclusion: Not original research. This is a systematic review and meta-analysis on the use of dexmedetomidine as a safe and effective drug for sedation for cardiac surgical patients. Not related to treatment of delirium.

Lingehall HC, Smulter N, Olofsson B, Lindahl E. Experiences of undergoing cardiac surgery among older people diagnosed with postoperative delirium: one-year follow-up. *BMC Nurs* 2015;14(1):1-10.

Reason for exclusion: Ineligible intervention. This is a qualitative study of a lived experience of those who experienced post cardiac surgery delirium. Not related to the pharmacological treatment of delirium.

Lingehall HC, Smulter NS, Lindahl E, Lindkvist M, Engström KG, Gustafson YG, Olofsson B. Preoperative cognitive performance and postoperative delirium are independently associated with future dementia in older people who have undergone cardiac surgery: a longitudinal cohort study. *Crit Care Med* 2017;45(8):1295-303.

Reason for exclusion: Ineligible outcome. This is a longitudinal study on cardiac delirium patients developing dementia post-surgery. Not related to the pharmacological treatment of delirium.

Liu H, Ji FH, Peng K, Applegate RL, Fleming N. Sedation after cardiac surgery: is one drug better than another? *Anaesth Analg* 2017;124(4):1061-70.

Reason for exclusion: Not original research. Ineligible outcome. This is a systematic review looking at what drug is the best drug to use for sedation post cardiac surgery. Not related to the pharmacological treatment of delirium.

Liu X, Xie G, Zhang K, Song S, Song F, Jin Y, Fang X. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. *J Crit Care* 2017;38:190-6.

Reason for exclusion: Not original research. This is a systematic review and meta-analysis on the use of dexmedetomidine vs propofol for sedation for cardiac surgical patients and the incidence of delirium. Not related to the pharmacological treatment of delirium.

Mailhot T, Cossette S, Cote J, Bourbonnais A, Cote MC, Lamarche Y, Denault A. A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study. *Nurs Crit Care* 2017;22(4):221-8.

Reason for exclusion: Ineligible intervention. This is a randomized pilot study using non-pharmacological strategies of family involvement in the management of post cardiac surgery delirium. Not related to the pharmacological treatment of delirium.

Maldonado JR, Wysong A. Postoperative sedation and the incidence of delirium and cognitive deficits in cardiac surgery patients. *Ann Neurol* 2003;54:S27-S8.

Reason for exclusion: Not original research. This is a supplementary on postoperative sedation and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Maldonado JR, Wysong A, van der Starre PJ, Block T, Reitz B. Postoperative sedation can dramatically alter the development of delirium after cardiac surgery. *Psychosomatics*. 2005;46(2):185-6.

Reason for exclusion: Not original research. This is an abstract on postoperative sedation and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Maldonado JR, Wysong A, van der Starre PJA, Block T, Miller C, Reitz BA. Is dexmedetomidine associated with a lower incidence of postoperative delirium when compared to propofol or midazolam in cardiac surgery patients. [Internet]. NCT00417664.2002 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT00417664>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial looking at the use of dexmedetomidine on the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium. Report obtained.

Maleva O, Trubnikova O, Barbarash O. Statins for the prevention of early postoperative cognitive dysfunction in patients undergoing coronary artery bypass grafting. *Eur Heart J* 2016;37:386.

Reason for exclusion: Not original research. This is an abstract of an RCT on the administration of statins in the early postoperative period and the impact on cognitive dysfunction. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mangusan RF, Hooper V, Denslow SA, Travis L. Outcomes associated with postoperative delirium after cardiac surgery. *Am J Crit Care* 2015;24(2):156-63.

Reason for exclusion: Ineligible outcome. This is a retrospective study on what was the effect of post cardiac surgery delirium on length of stay, cost, physio etc. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Maniar HS, Lindman BR, Escallier K, Avidan M, Novak E, Melby SJ, Damiano MS, Lasala J, Quader N, Rao RS, Lawton J, Moon MR, Helsten D, Pasque MK, Damiano RJ, Jr., Zajarias A. Delirium after surgical and transcatheter aortic valve replacement is associated with increased mortality. *J Thorac Cardiovasc Surg*. 2016;151(3):815-23.e2.

Reason for exclusion: Ineligible intervention. This is a retrospective study on the incidence of delirium post transcatheter aortic valve implantation surgery. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mardani D, Bigdelian H. The effect of dexamethasone prophylaxis on postoperative delirium after cardiac surgery: A randomized trial. *J Res Med Sci* 2012; 17(1 spl.1):S113-S9

Reason for exclusion: Ineligible intervention. This is an original report of an RCT on the prophylactic administration of dexamethasone in the preoperative and early postoperative period and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mariscalco G, Cottini M, Zanobini M, Salis S, Dominici C, Banach M, Onorati F, Piffaretti G, Covaia G, Realini M, Beghi C. Preoperative statin therapy is not associated with a decrease in the incidence of delirium after cardiac operations. *Ann Thorac Surg* 2012;93(5):1439-48.

Reason for exclusion: Ineligible intervention. This is a retrospective study on the prevention of postoperative delirium with the preoperative administration of statins. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mariscalco G, Mariani S, Biancari F, Banach M. Effects of statins on delirium following cardiac surgery - evidence from literature. *Psychiatr Pol* 2015;49(6):1359-70.

Reason for exclusion: Not original research. This is a literature review on the use of statins on the incidence of delirium in the postoperative patient. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Martin BJ, Buth KJ, Arora RC, Baskett RJ. Delirium: a cause for concern beyond the immediate postoperative period. *Ann Thorac Surg* 2012;93(4):1114-20.

Reason for exclusion: Ineligible outcome. This is a prospective study on the effects of perioperative delirium on patient outcomes. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mashour GA, Avidan MS. Postoperative delirium: disconnecting the network? *Anesthesiol* 2014;121(2):214-6.

Reason for exclusion: Not original research. This is an editorial on postop delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mathew JP, Sherman SK, White WD, Fitch JCK, Chen JC, Bell L, Newman MF. Preliminary report of the effects of complement suppression with pexelizumab on neurocognitive decline after coronary artery bypass graft surgery. *Stroke* 2004;35(10):2335-9.

Reason for exclusion: Ineligible intervention. This is a preliminary report of a phase II prevention clinical trial on the use of pexelizumab vs placebo and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, Burns KM, Thompson JL, Shintani AK, Ely EW, Pandharipande PP. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med* 2013;41(2):405-13.

Reason for exclusion: Ineligible outcome. This is a prospective study that explores modifiable risk factors. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mitchell SJ, Willcox T, Milsom FP, Gorman DF. Physical and pharmacological neuroprotection in cardiac surgery. *Semin Cardiothorac Vasc Anesth* 2000;4(2):80-5.

Reason for exclusion: Ineligible intervention. This is a literature review looking at the prevention of postoperative delirium with a focus on reducing air embolism from bypass. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Moll V, Ward CT, Zivot JB. Antipsychotic-induced neuroleptic malignant syndrome after cardiac surgery. *A Case Rep* 2016;7(1):5-8.

Reason for exclusion: Ineligible intervention. This is a case study about a patient's perspective on experiencing delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Mu J. Delirium in the Intensive Care Unit after Cardiac Surgery. Ann Arbor: J Chin Univ Hong Kong; 2015.

Reason for exclusion: Higher level study design located. Not an RCT. This paper is a thesis for a PhD. This is not a primary study related to pharmacological treatment of postop cardiac delirium

Mu JL, Lee A, Joynt GM. Pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery: systematic review and meta-analysis. *Crit Care Med* 2015;43(1):194-204.
Reason for exclusion: Not original research. Not a primary study. This is a systematic review and meta-analysis on pharmacological agents in the treatment of delirium. This systematic review does not include harms assessment.

Muellejans B, Matthey T, Scholpp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomized, open-label, pharmacoeconomic trial. *Crit Care* 2006; 10(3):R91
Reason for exclusion: Ineligible outcome. This is an RCT that compares remifentanil and propofol vs fentanyl and midazolam for sedation for cardiac surgical patients. Not related to the treatment of hyperactive delirium in the postoperative cardiac surgical patient. Focus is on sedation.

Muller A, Lachmann G, Wolf A, Morgeli R, Weiss B, Spies C. Peri- and postoperative cognitive and consecutive functional problems of elderly patients. *Curr Opin Crit Care* 2016;22(4):406-11.
Reason for exclusion: Not original research. Ineligible population. This is a systematic review on the management of delirium in the ICU. Not inclusive of cardiac surgical patients admitted into the ICU.

Nagapurkar US, Prasad BSV. Delirium in clinical practice. *Indian J Psychiatry* 2015;57(5):S167-S8.
Reason for exclusion: Not original research. This paper is a symposium on raising awareness of delirium and the need to manage it. Not related to pharmacological treatment of postop cardiac delirium.

Neelankavil J. Decreasing the incidence of delirium after cardiac surgery. [Internet]. NCT02119806. 2017 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02119806>
Reason for exclusion: Ineligible intervention. This is a clinical trial that commenced in January 2018. Appears to focus on prevention rather than pharmacological treatment of postop cardiac surgery delirium. No reporting of results available yet.

Newman MF. Statin therapy to limit cognitive dysfunction after cardiac surgery. [Internet]. NCT01186289. 2010 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT01186289>
Reason for exclusion: Ineligible intervention. This is a clinical trial that has been withdrawn due to a change in standard care being delivered. Unable to find a results/report paper. Author has been emailed but no response.

Norkiene I, Ringaitiene D, Kuzminskaitė V, Sipylaite J. Incidence and risk factors of early delirium after cardiac surgery. *Biomed Res Int* 2013;2013:323491.

Reason for exclusion: Ineligible outcome. This is a prospective cohort study on the incidence of delirium post cardiac surgery. Not related to pharmacological treatment of postop cardiac delirium.

Nour El-Din BM. Clinical evaluation of dexmedetomidine following ultra-fast track off-pump coronary artery bypass grafting. *Egypt J Anaesth* 2004;20(3):253-9.

Reason for exclusion: Ineligible intervention. This is an RCT on the use of dexmedetomidine vs midazolam for sedation. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Numan T, Slooter AJC, van der Kooij AW, Hoekman AML, Suyker WJL, Stam CJ, van Dellen E. Functional connectivity and network analysis during hypoactive delirium and recovery from anesthesia. *Clin Neurophysiol* 2017;128(6):914-24.

Reason for exclusion: Ineligible intervention. This is a prospective study that looks at neuro connectivity and function in the postop cardiac patient. Not related to pharmacological treatment of postop cardiac delirium.

Oh CS, Park S, Wan Hong S, Kang WS, Yoon TG, Kim SH. Postoperative delirium in patients undergoing off-pump coronary artery bypass grafting according to the anesthetic agent: a retrospective study. [J Cardiothorac Vasc Anesth](#). 2017 Dec;31(6):1988-1995.

Reason for exclusion: Ineligible intervention. This is a retrospective observational study that is looking at the incidence of delirium between the use of sevoflurane inhalation and propofol anesthesia. Not related to pharmacological treatment of postop cardiac delirium.

O'Neal J, Dighe S, Gray K, Lerner A, Talmor D, Marcantonio E, Subramaniam B. The use of dexmedetomidine and intravenous acetaminophen for the prevention of postoperative delirium in cardiac surgery patients over 60 years of age: A pilot study. *Anaesth Analg* 2015;120(3):S411.

Reason for exclusion: Ineligible intervention. This is a pilot study on the use of dexmedetomidine vs IV acetaminophen to prevent postoperative delirium. Not related to pharmacological treatment of postop cardiac delirium.

O'Neal JB, Liu X, Shotwell MS, Liang Y, Shaw A, Shah A, Billings FT. Impact of preoperative statin or beta blocker use and delirium following cardiac surgery. *Anaesth Analg* 2016;122(5):S57.

Reason for exclusion: Ineligible intervention. This is a retrospective study that is looking for an association between preoperative statin vs beta blocker medication administration and postop delirium. Not related to pharmacological treatment of postop cardiac delirium.

O'Neal JB, Shaw AD. Predicting, preventing, and identifying delirium after cardiac surgery. *Perioper Med* 2016;5.

Reason for exclusion: Not original research. This is a systematic review that focuses on predicting and identifying delirium in the postop cardiac patient. Not related to pharmacological treatment of postop cardiac delirium.

Oosterhouse KJ, Vincent C, Foreman MD, Gruss VA, Corte C, Berger B. Intensive care unit nurses' beliefs about delirium assessment and management. *AACN Adv Crit Care* 2016;27(4):379-93.

Reason for exclusion: Not original research. This is a literature review on the management of delirium in the postoperative patient. Not isolated to postoperative cardiac surgical patients.

Oosterhouse KJ, Vincent C, Foreman MD, Gruss VA, Corte C, Berger B. Delirium: a key challenge for perioperative care. *Int J Surg* 2013;11(2):136-44.

Reason for exclusion: Not original research. Ineligible population. This is a review paper on the management of delirium in the postoperative patient. Not isolated to postop cardiac surgical patients.

Osse RJ, Tulen JH, Hengeveld MW, Bogers AJ. Screening methods for delirium: early diagnosis by means of objective quantification of motor activity patterns using wrist-actigraphy. *Interact Cardiovasc Thorac Surg* 2009;8(3):344-8; discussion 8.

Reason for exclusion: Ineligible outcome. This is an observational study on the use of wrist actigraphy as a tool for early detection of delirium in the postop cardiac patient. Not related to pharmacological treatment of postop cardiac delirium.

Pandharipande P, Pun B, Herr D, Maze M, Girard T, Miller R, Shintani A, Thompson J, Jackson J, Deppen S, Stiles R, Dittus R, Bernard G, Ely E. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *Jama* 2007; 298(22):2644-53

Reason for exclusion: Ineligible intervention. This is a report of the MEND clinical trial of adult mechanically ventilated patients using a sedation strategy of dexmedetomidine \pm fentanyl versus lorazepam \pm fentanyl, on the incidence of delirium. Not related to pharmacological treatment of postop cardiac delirium.

Park JB, Bang SH, Chee HK, Kim JS, Lee SA, Shin JK. Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass.

Korean J Thorac Cardiovasc Surg 2014;47(3):249-54.

Reason for exclusion: Ineligible intervention. This prospective prevention study looked at the effectiveness of dexmedetomidine vs remifentanyl, commenced immediately postoperatively, on postoperative delirium. Not related to pharmacological treatment of postop cardiac delirium.

Parker RO, King AB, Hughes CG. Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in non-intubated patients. *J Thorac Dis* 2016;8(7):E596-E8.

Reason for exclusion: Not original research. Ineligible population. This is a commentary paper on the use of dexmedetomidine instead of haloperidol for the treatment of delirium in the ICU patient. Does not include ICU cardiac patient.

Pedersen SS, Jorgensen VL. Incidence, severity and treatment of delirium in cardiac surgery patients: a before-after study. [Internet]. NCT01774240. 2012 [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT01774240>

Reason for exclusion: Higher level study design located. This is a prospective cohort clinical trial. Not an RCT. Report paper written.

Pedersen SS, Kirkegaard T, Jorgensen MB, Jorgensen VL. Effects of a screening and treatment protocol with haloperidol on post-cardiotomy delirium: a prospective cohort study(dagger).

Interact Cardiovasc Thorac Surg;18(4):438-45.

Reason for exclusion: Higher level study design located. This is a prospective cohort study on screening and treatment protocol using haloperidol. Not an RCT. This paper relates to NCT01774240.

Perrault LP, Denault AY, Carrier M, Cartier R, Belisle S. Torsades de pointes secondary to intravenous haloperidol after coronary bypass grafting surgery. *Can J Anaesth* 2000;47(3):251-4.

Reason for exclusion: Not original research. This is a clinical report on the harms of using haloperidol and the development of Torsades de point. Not related to pharmacological treatment of postop cardiac delirium.

Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: a randomized placebo-controlled trial. *Br J Anaesth* 2011;106(6):873-81.

Reason for exclusion: Ineligible intervention. This is an RCT on the use of pregabalin vs placebo for the reduction of pain, avoiding the use of opioids. Not related to pharmacological treatment of postop cardiac delirium.

Pollari F, Santarpino G, Fischlein T. A lot of drugs and not much oxygen: is the cocktail responsible for delirium? *J Thorac Cardiovasc Surg* 2014;147(4):1438-9.

Reason for exclusion: Not original research. This is a letter to the editor on the use of near-infrared spectroscopy in monitoring for delirium. Not related to pharmacological treatment of postop cardiac delirium.

Popeo DM. Delirium in older adults. *Mt Sinai J Med* 2011;78(4):571-82.

Reason for exclusion: Not original research. Ineligible population. This is a clinical review. Not a primary study. Not isolated to postop cardiac patients only. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Popp J, Arlt S. Prevention and treatment options for postoperative delirium in the elderly. *Curr Opin Psychiatry* 2012;25(6):515-21.

Reason for exclusion: Not original research. Ineligible population. This is a systematic review that looks at both prevention and treatment of delirium. Not a primary study. Not isolated to postop cardiac patients only.

Power-Murrin M, Rodgers P. Delirium in critical care: a critical problem. There is little confusion about that! *Dynamics* 2006;17(2):35-6.

Reason for exclusion: Not original research. This is a published abstract. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care* 2007;35(5):714-9.

Reason for exclusion: Ineligible intervention. This RCT is a prevention trial on the use of risperidone to prevent postoperative delirium after cardiac surgery. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Priye S, Jagannath S, Singh D, Shivaprakash S, Reddy DP. Dexmedetomidine as an adjunct in postoperative analgesia following cardiac surgery: a randomized, double-blind study. *Saudi J Anaesth* 2015;9(4):353-8.

Reason for exclusion: Ineligible intervention. This is an RCT on the effectiveness of dexmedetomidine in relieving pain in the postop cardiac patient. Not related to pharmacological treatment of postop cardiac delirium.

Reardon DP, Anger KE, Adams CD, Szumita PM. Role of dexmedetomidine in adults in the intensive care unit: an update. *Am J Health Syst Pharm* 2013;70(9):767-77.

Reason for exclusion: Not original research. Ineligible population. This is a review paper on the management of delirium in the postoperative patient. Not isolated to postop cardiac surgical patients.

Redelmeier DA, Thiruchelvam D, Daneman N. Delirium after elective surgery among elderly patients taking statins. *Can Med Assoc J* 2008;179(7):645-52.

Reason for exclusion: Ineligible intervention. This is a retrospective cohort study on the effect of statins on the incidence of delirium in the post cardiac surgical patient. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Ricksten SE. Cerebral dysfunction after cardiac surgery - Are we moving forward? *Curr Opin Anaesthesiol* 2000;13(1):15-9.

Reason for exclusion: Not original research. This is a review paper on the effects of cardiac surgery on postoperative delirium. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Roberts R. Preventing PPD after surgery...post pump delirium. J Clin Pract Educ Manag 1991;4(27):28-31.
Reason for exclusion: Not original research. This is a clinical expert article on the nurses' role to prevent postoperative delirium after cardiac surgery. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Royse C, Andrews D, Newman S, Stygall J, Williams Z, Pang J, Royse A. The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. Anaesthesiol 2011; 66(6):455-64.

Reason for exclusion: Ineligible intervention. This prevention RCT looked at propofol vs desflurane as anesthetic agents and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Royse C, Saager L, Whitlock R, Ou-Young J, Royse A, Vincent J, Devereaux P, Kurz A, Awais A, Panjasawatwong K, Sessler D. Impact of methylprednisolone on postoperative quality of recovery and delirium in the steroids in cardiac surgery trial: a randomized, double-blind, placebo-controlled substudy. Anesthesiol 2017;126(2):223-33.

Reason for exclusion: Ineligible intervention. This prevention RCT looked at methylprednisolone on induction and then again prior to cardiopulmonary bypass vs placebo and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Rudolph JL. Delirium after cardiac surgery. In: Katlic MR, ed. Cardiothoracic Surgery in the Elderly. New York: Springer,2011; 57-66.

Reason for exclusion: Not original research. This is a book chapter. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Sanders RD, Pandharipande PP, Davidson AJ, Ma DQ, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. BMJ 2011; Jul 20(343):d4331.

Reason for exclusion: Not original research. Ineligible population. This is a review paper on the management of delirium in the postoperative patient. Not isolated to postop cardiac surgical patients.

Sauer AM, Slooter AJ, Veldhuijzen DS, van Eijk MM, Devlin JW, van Dijk D. Intraoperative dexamethasone and delirium after cardiac surgery: a randomized clinical trial. *Anesth Analg*. 2014;119(5):1046-52.
Reason for exclusion: Ineligible intervention. This is an RCT that looks at the use of dexamethasone administration intraoperatively to reduce the incidence and duration of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Schoen J, Husemann L, Tiemeyer C, Lueloh A, Sedemund-Adib B, Berger KU, Hueppe M, Heringlake M. Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: A randomized controlled trial. *Br J Anaesth* 2011;106(6):840-50.
Reason for exclusion: Ineligible intervention. This is an RCT that looks at the use of sevoflurane vs propofol and the incidence of delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Scolletta S, Taccone FS, Donadello K. Brain injury after cardiac surgery. *Minerva Anestesiol* 2015;81(6):662-77.
Reason for exclusion: Not original research. This is a review paper on brain injury in the postoperative cardiac surgical patient. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Scott DA, Evered LA, Silbert BS. Cardiac surgery, the brain, and inflammation. *J Extra Corpor Technol* 2014;46(1):15-22.
Reason for exclusion: Not original research. This is an expert review about the concerns and concepts of postoperative cardiac surgery delirium. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Segatore M, Dutkiewicz M, Adams D. The delirious cardiac surgical patient: theoretical aspects and principles of management. *J Cardiovasc Nurs* 1998;12(4):32-48.
Reason for exclusion: Not original research. This is a clinical management paper. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Serafim RB, Soares M, Bozza FA, Silva J, Dal-Pizzol F, Paulino MC, Povoá P, Salluh JIF. Outcomes of subsyndromal delirium in ICU: a systematic review and meta-analysis. *Crit Care*. 2017 Jul 12;21(1):179.
Reason for exclusion: Not original research. Ineligible population. This is a systematic review. Not a primary study. Not isolated to postoperative cardiac patients. Not related to the pharmacological treatment of postoperative cardiac surgery delirium. Focus on subsyndromal delirium rather than hyperactive delirium.

Serafim RB, Bozza FA, Soares M, do Brasil P, Tura BR, Ely EW, Salluh JIF. Pharmacologic prevention and treatment of delirium in intensive care patients: a systematic review. *J Crit Care* 2015;30(4):799-807.
Reason for exclusion: Ineligible population. Not original research. This is a systematic review of pharmacological management of delirium. Not related to the pharmacological treatment of postoperative cardiac surgery delirium. Not isolated to postoperative cardiac patients.

Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, Chen J. Prevalence of delirium with dexmedetomidine compared with morphine-based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiol* 2009;111(5):1075-84.
Reason for exclusion: Ineligible intervention. This is a prevention RCT that compares the administration of dexmedetomidine vs morphine for analgesia and sedation in the postoperative period after cardiac surgery and the incidence of delirium. Not related to the pharmacological treatment of postoperative cardiac surgery delirium.

Shehabi Y, Green M, Taylor N, Beaudoin M, Grant P, Bailey M, Endre Z. The safety and efficacy of perioperative dexmedetomidine in cardiac surgery. *Anaesth Analg* 2016;123(3):167.
Reason for exclusion: Not original research. This is a supplementary article that looks at the use of dexmedetomidine on the postoperative cardiac surgical patient. Not related to the pharmacological treatment of postoperative cardiac surgery delirium and is based on prevention.

Sheu R, Cormican D, McConnell M. Con: Dexmedetomidine sedation should not be used Routinely for all post-cardiac surgical patients in the intensive care unit. *J Cardiothorac Vasc Anesth* 2016;30(5):1422-4.
Reason for exclusion: Not original research. This review article looks at the use of dexmedetomidine on the postoperative cardiac surgical patient. Not related to the pharmacological treatment of postoperative cardiac surgery delirium.

Shora H, Amr Y, Sherief S. Prospective study on the effect of inhalational versus intravenous sedation on delirium and agitation in patients admitted to ICU postcardiac surgery. *J Cardiothorac Vasc Anesth* 2016; 30(1):S34.

Reason for exclusion: Not original research. This article is a published abstract on a prevention prospective study looking at inhaled sedation vs IV sedation and the effect on the incidence of delirium. Not related to the pharmacological treatment of postoperative cardiac surgery delirium.

Shu A, Liu X, Wang Q, Chen X, Zhan L. Study on cerebral protective effect of dexmedetomidine during anesthesia in cardiac valve replacement surgery. *Int J Clin Exp Med* 2017; 10(1):1066-72.

Reason for exclusion: Ineligible intervention. This prevention RCT looked at the effect of dexmedetomidine vs placebo on the incidence of delirium. Not related to the pharmacological treatment of postoperative cardiac surgery delirium.

Smith B. Delirium issues in elderly surgical patients. *AORN J* 2012;96(1):75-85.

Reason for exclusion: Ineligible population. Not original research. This is a review paper on delirium in postoperative surgical elderly patient. Not related to the pharmacological treatment of postoperative cardiac surgery delirium. Not isolated to postoperative cardiac patients.

Sockalingam S, Parekh N, Bogoch II, Sun J, Mahtani R, Beach C, Bollegalla N, Turzanski S, Seto E, Kim J, Dulay P, Scarrow S, Bhalerao S. Delirium in the postoperative cardiac patient: a review. *J Card Surg* 2005;20(6):560-7.

Reason for exclusion: Not original research. This is a review paper on delirium in postoperative cardiac surgical patient. Not related to the pharmacological treatment of postoperative cardiac surgery delirium. Not a primary study.

Syed S. Benzodiazepine-free anesthetic for reduction of delirium (B-Free). [Internet]. NCT03053869. 2017 [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT03053869>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. This clinical trial is still in progress. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Spies C. Neuroprotection with dexmedetomidine in patients undergoing elective cardiac or abdominal surgery (NEURODEX). [Internet]. NCT02096068. 2014. [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02096068>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Currently in progress. No reporting of results available yet. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Spithouraki E, Nieri AS, Manousaki K. Dexmedetomidine and risperidone for the reduction of delirium after cardiac surgery: systematic review. Eur J Cardiovasc Nurs 2016;15:S51.

Reason for exclusion: Not original research. Not a primary study. This is a systematic review on the effect of dexmedetomidine and risperidone in reducing the incidence of delirium. Not related to pharmacological treatment of postop cardiac delirium.

Steiner LA. Rivastigine for the prevention of postoperative delirium in the elderly undergoing cardiac surgery. [Internet]. NCT00257868. 2005. [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT00257868>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Results have been published. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Strom C, Rasmussen LS, Sieber FE. Should general anesthesia be avoided in the elderly? Anaesth 2014;69:35-44.

Reason for exclusion: Ineligible population. Not original research. This is a review paper that is questioning whether the elderly should avoid general anesthesia for surgery. Not specific to cardiac surgery. Not a primary study.

Subramaniam B. The use of dexmedetomidine and intravenous acetaminophen for the prevention of postoperative delirium in cardiac surgery patients over 60 years of age: a pilot study. [Internet]. NCT02546765. 2015. [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT02546765>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Results have been published. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Summers, 1979. Psychiatric sequelae to cardiectomy. J Cardiovasc Surg 1979;20(5):471-6.

Reason for exclusion: Ineligible outcome. This is a pilot study on the incidence and risk factors for psychiatric syndrome post cardiac surgery. Not related to pharmacological intervention for the treatment of postop delirium.

Sweitzer NK. A randomized, placebo-controlled, double blind evaluation of the safety and efficacy of angiotensin 1-7 (Ang-(1-7)) to enhance cognitive function in participants undergoing coronary artery bypass graft (CABG) surgery. [Internet]. NCT03252093. 2017. [cited 2017 December 12]. Available from

<https://clinicaltrials.gov/ct2/show/NCT03252093>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Currently recruiting. Results have not yet been published. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Tagarakis GI, Tsolaki-Tagaraki F, Tsolaki M, Diegeler A, Tsilimingas NB, Papassotiropoulos A. The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations. Am J Alzheimers Dis Other Demen. 2007; 22(3):223-8.

Reason for exclusion: Ineligible outcome. This is a prospective study looking at a genetic link to postoperative delirium. Not related to pharmacological treatment of postop cardiac delirium.

Tagarakis GI. Neurotological disorders and neuroprotection after heart surgery. Recent Pat CNS Drug Discov 2008;3(3):226-9.

Reason for exclusion: Not original research. This is a review paper on the effect of pharmacological agents and the incidence of delirium. Not a primary study. Not related to the treatment of postop cardiac surgery delirium.

Taipale P, Ratner P, Galdas P, Jillings C, Manning D, Fernandes C, Gallaher J. Analgesia, and sedation following cardiac surgery: An association with delirium? Can J Cardiol 2011;27(5):S348.

Reason for exclusion: Not original research. This is a supplementary abstract on the effect on delirium risk associated with the use of opiates and sedation. Not related to pharmacological treatment of postop cardiac delirium.

Taipale PG, Ratner PA, Galdas PM, Jillings C, Manning D, Fernandes C, Gallaher J. The association between nurse-administered midazolam following cardiac surgery and incident delirium: an observational study. *Int J Nurs Stud* 2012;49(9):1064-73.

Reason for exclusion: Ineligible intervention. This observational study looked at the incidence of delirium with nurse-initiated administration of midazolam. Not related to pharmacological treatment of postop cardiac delirium.

Tanigami H, Yahagi N, Kumon K, Watanabe Y, Haruna M, Matsui J, Hayashi H. Long-term sedation with isoflurane in postoperative intensive care in cardiac surgery. *Artif Organs* 1997; 21(1):21-3.

Reason for exclusion: Ineligible intervention. This retrospective study looked at the effectiveness and harm of isoflurane vs fentanyl/midazolam on long term sedation. Not related to pharmacological treatment of postop cardiac delirium.

Tesar GE, Hackett TP. Psychiatric management of the hospitalized cardiac patient. *J Cardiopulm Rehabil* 1985;5(5):219-25.

Reason for exclusion: Not original research. This is a clinical management paper. Not a primary study. Not related to pharmacological treatment of postop cardiac delirium

Theuerkauf N, Guenther U, Putensen C. Postoperative delirium in the PACU and intensive care unit. *Curr Anaesth Crit Care* 2012;2(4):148-55.

Reason for exclusion: Not original research. Ineligible population. This is a systematic review. Not a primary study. Not isolated to postop cardiac patients only. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Tremblay P, Gold S. Prevention of post-operative delirium in the elderly using pharmacological agents. *Can Geriatr J* 2016;19(3):113-26.

Reason for exclusion: Not original research. Not a primary study. This is a review paper on the use of pharmacological agents to prevent delirium in the cardiac surgical patient. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Tsaryanski G, Tenev B, Cholacov V, Markovski A, Abedinov F, Baev B, Petkov D, Iliev R, Nachev G. Cardiac surgery in octogenarians: Postoperative morbidity and mortality. *Heart Surg Forum* 2012;15(6):E356.

Reason for exclusion: Higher level study design located. This is a case study on right coronary artery aneurysm management. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Trivedi A. A comparative study of dexmedetomidine and midazolam in reducing delirium caused by ketamine. *J Clin Diagn Res* 2016; 10(8):Uc01-uc4.

Reason for exclusion: Ineligible intervention. This is a comparative study on the use of dexmedetomidine and midazolam when sedating compared with ketamine that causes delirium. Not related to pharmacological treatment of postop cardiac delirium.

Vallabhajosyula S, Kanmanthareddy A, Erwin PJ, Esterbrooks DJ, Morrow LE. Role of statins in delirium prevention in critical ill and cardiac surgery patients: A systematic review and meta-analysis. *J Crit Care* 2017; Feb(37):189-196.

Reason for exclusion: Not original research. Ineligible intervention. This is a systematic review and meta-analysis on prevention of delirium. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Van der Starre P, Maldonado J, Wysong A, Miller C, Reitz B. Dexmedetomidine prevents delirium after cardiac surgery. *Eur J Anaesthesiol* 2009;26:3.

Reason for exclusion: Not original research. This is a published abstract paper on prevention of delirium with the use of dexmedetomidine. Not a primary study. Not related to pharmacological treatment of postop cardiac delirium.

van Dijk D. Postoperative cognitive dysfunction -- what is the clinical relevance? *Acta Anaesthesiol Scand* 2009;53:29-30.

Reason for exclusion: Ineligible outcome. This study re: the long-term effect of postoperative delirium and the relevance to reduce incidence. Not related to pharmacological treatment of postop cardiac delirium.

van Eijk MM, Slooter AJ. Delirium in intensive care unit patients. *Semin Cardiothorac Vasc Anesth.* 2010;14(2):141-7.

Reason for exclusion: Not original research. This paper is an expert review on delirium in the postop cardiac patient. Not related to pharmacological treatment of postop cardiac delirium.

Vasquez E, Chitwood WR, Jr. Postcardiotomy delirium: an overview. *Int J Psychiatry Med.* 1975;6(3):373-83.

Reason for exclusion: Not original research. This is a review paper. Ineligible population. Not a primary study. Not isolated to postop cardiac patients only. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Walther S. Dexmedetomidine for the treatment of delirium after heart surgery. [Internet]. NCT01140529. 2010. [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT01140529>

Reason for exclusion: This was a clinical trial that was withdrawn due to slow recruitment. Unable to find a results/report paper.

Wanat M, Fitousis K, Boston F, Masud F. Comparison of dexmedetomidine versus propofol for sedation in mechanically ventilated patients after cardiovascular surgery. *Methodist Debaque Cardiovasc J* 2014;10(2):111-7.

Reason for exclusion: Ineligible intervention. Ineligible outcome. This is a retrospective observational study that looks at the comparison of propofol with dexmedetomidine for sedation post coronary artery bypass grafting surgery. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum A, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomized, double-blind, placebo-controlled trial. *Lancet* 2015;386(10000):1243-53.

Reason for exclusion: Ineligible intervention. This was a prevention RCT. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Wittwer ED. The impact of ketamine on postoperative cognitive dysfunction, delirium, and renal dysfunction in patients 75 years of age or older and undergoing cardiac surgery. [Internet]. NCT02554253. 2015. [cited 2017 December 12]. Available from <https://clinicaltrials.gov/ct2/show/NCT02554253>

Reason for exclusion: Ineligible intervention. This clinical trial is a prevention trial. Currently in progress. No reporting of results available yet. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Wong JK, Nikravan S, Maxwell BG, Marques MA, Pearl RG. Nocturnal low-dose propofol infusion for the management of icu delirium: a case series in non-intubated cardiac surgery patients. J Cardiothorac Vasc Anesth 2016;30(5):1340-3.

Reason for exclusion: Higher level study design located. This is a case study on a patient's perspective on experiencing delirium. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Yazigi A, Madi-Jebara S, Haddad F, Hayek G. Cholinesterase inhibitors and delirium after cardiac surgery. Crit Care Med 2010;38(4):1231.

Reason for exclusion: Not original research. This is a letter to the editor. Not a primary study. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Zakharov V, Hussain A, Smetkin A, Kirov M. Comparison of sevoflurane and propofol anesthesia. Eur J Anaesthesiol 2014;31:120

Reason for exclusion: Ineligible intervention. This is an RCT that compares propofol with sevoflurane anesthesia for CABG and the effect on cerebral oxygenation. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Zhai W, Liu J, Si Y, Han J. Changes in postoperative cognitive function during off-pump coronary artery bypass graft surgery: Dose response of propofol. Int J Clin Exp Med 2016;9(6):10939-46.

Reason for exclusion: Ineligible intervention. This was an RCT that looked at the concentration of propofol and its effect on cognitive dysfunction in the postop cardiac patient. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Zhang XY, Zhao X, Wang YW. Dexmedetomidine: a review of applications for cardiac surgery during perioperative period. J Anesth 2015;29(1):102-11.

Reason for exclusion: Not original research. Not a primary study. This is a review paper on the use of dexmedetomidine in the cardiac surgical patient. Not related to the pharmacological treatment of postop cardiac surgery delirium.

Appendix III: Characteristics of included studies

Study	Study design	Participants	Intervention	Comparator	Length of follow-up	Outcomes
Atalan et al. 2013	Prospective RCT	n=53 (Group 1 n=26, Group 2 n=27)	The intervention group received 5mg morphine IM hourly until adequate sedation and a RASS score between -1 to +1 was achieved. Once the 20mg dose had been administered and the patient remained agitated then 2.5mg lorazepam BD was administered per-oral was added to the treatment regime.	The comparator group received 5mg haloperidol IM hourly until adequate sedation and a RASS score between -1 to +1 was achieved. Once the 20mg dose had been administered and the patient remained agitated then 2.5mg lorazepam BD was administered per-oral was added to the treatment regime.	unknown	It was determined that the patients who were receiving morphine treatment responded more quickly compared with the haloperidol treatment group. The overall results showed that 8 patients in Group 2 (haloperidol group) received additional sedatives compared with 1 patient in Group 1.
Tagarakis, 2012	Prospective RCT	n=80 (Group 1 n=40, Group 2 n=40)	The intervention group was given 8mg of ondansetron IV and were evaluated before and 10 mins after the injection with a 4-point scale for the detection and evaluation of delirium.	The comparator group was given 5mg of haloperidol IV and were evaluated before and 10 mins after the injection with a 4-point scale for the detection and evaluation of delirium.	unknown	Both ondansetron and haloperidol had excellent and equal delirium controlling effects, without statistically significant differences.
Yapici, 2010	Prospective RCT	n=72 (Group 1 n=34, Group 2 n=38)	The intervention group received a 0.3-0.7micrograms/kg/hr of dexmedetomidine IV. After the	The comparator group received 0.05-0.2mg/kg/hr of midazolam intravenously to control delirium.	unknown	Dexmedetomidine administration in this study caused the disappearance

Study	Study design	Participants	Intervention	Comparator	Length of follow-up	Outcomes
			<p>initiation of dexmedetomidine treatment, the background sedation of fentanyl and midazolam were weaned off and ceased. The dexmedetomidine dose was titrated on the basis of the patients' heart rate and blood pressure response.</p>	<p>Some patients in this group received haloperidol 5mg IM 4 times per day for treatment of agitation as well as other drugs such as benzodiazepines, haloperidol or atypical antipsychotics.</p>		<p>of delirium symptoms and led to shorter times to extubation, without haemodynamic disturbance. Dexmedetomidine can be a good choice for the management of the delirium state associated with prolonged mechanical ventilation after cardiac surgery.</p>

Abbreviations: RASS – Richmond agitation sedation scale, BD – twice daily, IV – intravenous, IM – intramuscular, mg – milligram, mcg – microgram, kg – kilogram, hr – hour, mins - minutes