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| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | 1 |
| **ABSTRACT**  |  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | 2 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 5 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 5 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 6 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 6 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 6 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 6/Appendix |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 6 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 6-8 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 6-7 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | - |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 7-8 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | 7-8 |

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| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | - |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | - |
| **RESULTS**  |  |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | 9 + fig 1 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | 9-11 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | - |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 11-13 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 11-13 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | - |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | - |
| **DISCUSSION**  |  |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | 14 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 15 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 15-16 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | - |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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*Supplementary Material 2:*

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*Pearl growing strategy used to formulate a formal search strategy on Ovid MEDLINE and Cochrane*

*Supplementary Material 3:*

|  |  |
| --- | --- |
| 1. | \*Delirium/pc |
| 2. | postoperative delirium.mp. |
| 3. | or/1-2 |
| 4. | Randomized Controlled Trials as Topic |
| 5. | systematic review.ti. |
| 6. | meta-analysis.ti. |
| 7. | or/4-6 |
| 8. | 3 and 7 |
| = | 115 RESULTS |

*Formal search strategy conducted on Ovid MEDLINE on 30 September 2019.*

*Supplementary Material 4:*

|  |  |
| --- | --- |
|  | Number of Results |
| 1.  | (post\*operative):ti,ab,kw AND (delirium):ti,ab,kw | 10 |
| 2.  | MeSH descriptor: [Delirium] explode all trees | 603 |
| 3.  | #1 AND #2 | **6** |

*Formal search strategy conducted on Cochrane Library advanced search (search manager) on 4 October 2019.*

***Supplementary Material 5:****Initial data extraction table with information including: primary research article citation; specific intervention examined; time of intervention compared to surgery (pre-, intra-, post-, and peri-operative); hypothesised mechanism of action (MoA); and, outcome in terms of incidence of POD (if no reduction in POD incidence found then written in red text). Classification of mechanism of action was also included.*

*NB: Red writing = either no reduction in POD incidence found, or MoA not found. Blue writing = Classified MoA decided by EB, black writing for classification agreed upon by EB, RB, MW, DH and ML). Green writing = positive reduction in incidence of POD with Dexmedetomidine intervention. Orange writing = other sources used/notes to EB.*

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| **Intervention (POST-OPERATIVE)** | **Hypothesised Mechanisms of Action** | **Classification of MoA** |
| “Delirium-free protocol: Intramuscular injection of diazepam at 20:00 h each night, as well as a continuous intravenous infusion of flunitrazepam and pethidine administered over 8 h, for the first three nights postoperatively”. | “Artificial control of the sleep-awake rhythm by medication to overcome insomnia experienced by majority of patients experiencing post operative delirium”1. | Re-enforcing sleep-wake cycle |
| 2.5mg intravenous Haloperidol (antipsychotic) administered for 3 days postoperatively.NB: Fukata et al found that this was not effective at reducing incidence of POD.  | “Prophylactic Antipsychotic medication use”2. [Dopamine antagonist] | Targeted pharmacological therapy for dysregulation of neuronal activity |
| 5mg Intravenous Haloperidol (antipsychotic) administered at 21:00hrs on first day postoperatively. | “Prophylactic antipsychotic medication use, furthermore Haloperidol found to help regulate sleep-wake cycle”3.  | Targeted pharmacological therapy for dysregulation of neuronal activityRe-enforcing sleep-wake cycle |
| Music Therapy, 1 hour per day for 4 days. NB: McCaffrey found a significant reduction in incidence of POD on day 1 of therapy, but no difference by day 3.  | “Music listening is a passive activity that does not require a person's attentiveness but rather facilitates a nonthreatening atmosphere and provides an environment for healing. Music is effective in improving cognition as well. Music has been shown to be effective in calming persons who are agitated, which is often a sign of delirium”4. | Anxiolysis (non-pharmacological) |
| Parecoxib (40 mg dissolved in 5 ml saline at end of surgery, and then every 12 hours for 3 days) supplementary to morphine analgesia. | “Severe pain and high-dose opioids are both associated with increased risk of postoperative delirium, Parecoxib supplementation may mitigate these effects”5.  | Optimising analgesiaReducing delirium-inducing medication |
| Dexmedetomidine – initial bolus of 0.4 μg/kg dexmedetomidine followed by an infusion of 0.2 to 0.7 mcg/kg/−h−1 for up to 24 hours vs. propofol infusion 25 to 50 mcg/kg/min−1until readiness for tracheal extubation.Djaiani and team found Dexmedetomidine “to reduce incidence, delay onset, and shorten duration of POD in elderly patients after cardiac surgery, when compared with propofol. | “Dexmedetomidine has a unique mechanism of action exhibiting sedative, anxiolytic, and analgesic effects without causing respiratory depression.15 Furthermore, dexmedetomidine improves the quality of sleep in critically ill patients,16 primarily resembling a nonrapid eye movement sleep pattern.17 As an α2-adrenergic receptor agonist, it has also been shown to have significant opioid-sparing effect.18 In addition, dexmedetomidine is lacking clinically significant anticholinergic effects15 and has been shown to attenuate the inflammatory response of cardio-pulmonary bypass.19 A combination of all of these unique properties of dexmedetomidine may have contributed to the reduced incidence and duration of POD”6. | Optimising analgesiaReducing delirium-inducing medicationReducing inflammatory responseRe-enforcing Sleep-wake cycle |
| Received one of 3 post-operative sedation regimens: dexmedetomidine, propofol or midazolam.Maldonado found reduction in incidence for POD with Dex:“The findings of this open-label, randomized clinical investigation suggest that postoperative sedation with dexmedetomidine was associated with significantly lower rates of postoperative delirium and lower care costs.” | “Sedation with [dexmedetomidine](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/dexmedetomidine) may be associated with a lower incidence of delirium, given its particular pharmacological properties: it is not a GABAergic agent, and it has no [anticholinergic effects](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/anticholinergic-effect); it produces sedation, and promotes amore physiological sleep pattern without significant [respiratory depression](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/respiration-depression), and it has been reported to be associated with a decreased need for [opioid](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/psychology/opioid) use”7. | Re-enforcing sleep-wake cycleReducing delirium-inducing medicationOptimising analgesia |
| Cyproheptadine 4mg, 3x a day for 7 days. | “Excessive activation of the serotonergic system may lead to or aggravate delirium. Cyproheptadine may decrease postoperative delirium because of inhibition of serotonin receptors”8.  | Targeted pharmacological therapy for dysregulation of neuronal activity |
| 4 ml of intravenous Ondansetron 8 mg for five days post operatively9. | NR: Could not find paper in full-text.  | Targeted pharmacological therapy for dysregulation of neuronal activity |
| Dexmedetomidine (loading dose, 0.5 mcg/kg; maintenance dose, 0.2 to 0.8 mcg/kg/hr) vs Remifentanil (range, 1,000 to 2,500 mcg/hr).Park found:“When the delirium incidence was compared with the dexmedetomidine group (6 of 67 patients, 8.96%) and the remifentanil group (17 of 75 patients, 22.67%) it was found to be significantly less in the dexmedetomidine group (p<0.05).” | “Dexmedetomidine is a highly selective and potent α-2 adrenergic agonist with sedative and analgesic properties that produces sedation with modest analgesic and possible anti-delirium effects with minimal respiratory depression. Dexmedetomidine has the ability to provide adequate postoperative sedation and analgesia without producing excessive hypotension or the need for vasopressors, while reducing the risk of delirium after cardiac surgery. Unlike conventional sedatives such as propofol, midazolam, or morphine, dexmedetomidine can produce anxiolysis and sedation without provoking significant respiratory depression. It seems that this respiratory advantage of dexmedetomidine is directly related to postoperative delirium, as other studies have implied that dexmedetomidine’s effects on delirium are not simply due to its opioid-sparing properties. Several studies have reported that prolonged periods of intubation increase the risk of delirium by 1.10 to 7.90 times as compared to shorter periods of intubation. Consequently, dexmedetomidine has another potential advantage in that patients may be extubated in the sedated state and that they may be maintained under sedation as long as necessary until homeostasis is recovered and pain and anxiety are kept under control”10. | Optimising analgesiaReducing delirium-inducing medicationTargeted pharmacological therapy for dysregulation of neuronal activity |
| Post-operative 12 h infusion of dexmedetomidine 0.4 μg/kg/h without a loading dose vs placebo.Priye found:“Incidence of delirium was less in dexmedetomidine group (P = 0.086+).”Along with less opioids used in the Dexmedetomidine group. | “In contrast to the gamma-amino butyric acid agonists and opiates, dexmedetomidine has a unique mechanism of action. It combines sedative, anxiolytic, sympatholytic, anti-delirious and analgesic sparing properties with minimal respiratory depression. Although the exact mechanism by which dexmedetomidine counteracts agitation remains unclear, animal models show an increase in acetylcholine and reduction in noradrenaline levels in cerebrospinal fluid in response to dexmedetomidine, suggesting a central nervous system mediated effect”11. | Optimising analgesia.Reducing delirium-inducing medicationTargeted pharmacological therapy for dysregulation of neuronal activity |
| 1 mg of risperidone or placebo sublingually when they regained consciousness12. | “Risperidone is a second generation anytipsychotic in the chemical class of benzisoxazole derivatives. It it proposed to work by mediating a combination of dopamine type 2 and serotonin type 2 receptor antagonism12.”  | Targeted pharmacological therapy for dysregulation of neuronal activity |
| L-tryptophan, 1g orally three times a day or placebo was started after surgery and continued for up to 3 days postoperatively.NB: Robinson et al found no difference in incidence of POD between the intervention and control groups.  | “Tryptophan is an amino acid precursor to the delirium-relevant neurotransmitters serotonin and melatonin. The final neurotransmitter in the tryptophan metabolism pathway is melatonin which a sedating neurotransmitter and causes drowsiness. Tryptophan homeostasis is well described to be disrupted in the post-operative setting. Our work in addition to that of others, found lower post-operative levels of tryptophan in patients who develop delirium”13. | Targeted pharmacological therapy for dysregulation of neuronal activity.Re-enforcing sleep-wake cycle.  |
| Donepezil Hydrochloride (Aricept) 5mg immediately following surgery and every 24 h thereafter for a further three days14.NB: Sampson found no significant reduction in POD with this treatment, however found that some beneficial trend.  | Aricept (donepezil hydrochloride) is a cholinesterase inhibitor that reduces or prevents acetylcholine breakdown in brain tissue. Aricept is used to treat mild to moderate dementia like that found in patients with Alzheimer's disease. Cholinergic systems are involved in cognition, arousal and sensory gating. Total serum anticholinergicity has consistently been shown to be associated with delirium in older patients. Therefore augmentation of cholinergic function would, theoretically, present itself as a target for intervention with a view to reducing both the incidence and severity of delirium. Cholinesterase inhibitors increase the synaptic availability of ACh and donepezil hydrochloride is of proven efficacy in the treatment of moderately severe Alzheimer’s disease.NB: The above taken from Google.  | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Dexmedetomidine (0.1-0.7 mcg/kg/ml) or morphine (10-70 mcg/kg/ml) both at 3ml/h to maintain target sedation and analgesia15.NB: Shehabi et al found no significant reduction in incidence of POD, however did see positive outcomes for duration of POD/early extubation/less systolic hypotension with dexmedetomidine.  | N/A didn’t give MoA just that others found it helpful.  | Optimising analgesia. |
| Intravenous dexmedetomidine (0·1 μg/kg per h, from intensive care unit admission on the day of surgery until 0800 h on postoperative day 1), or placebo.Su found:“The incidence of postoperative delirium was significantly lower in the dexmedetomidine group (32 [9%] of 350 patients) than in the placebo group (79 [23%] of 350 patients; odds ratio [OR] 0·35, 95% CI 0·22-0·54; p<0·0001).” | “Dexmedetomidine is a highly selective α2 adrenoreceptor agonist that provides anxiolysis, sedation, and modest analgesia with minimal respiratory depression.In previous studies, dexmedetomidine was compared with an active sedative drug that modulates the γ-aminobutyric-acid type A (GABAA) receptors. These modulators of GABAA receptors, exemplified by benzodiazepines, could increase the prevalence of delirium.Another plausible explanation is that dexmedetomidine does not prevent the occurrence of delirium, but also does not increase the prevalence of delirium as do modulators of the GABAA receptors. Night-time infusion of sedative dose dexmedetomidine improved sleep quality in mechanically ventilated ICU patients”16. | Re-enforcing sleep-wake cycleReducing delirium-inducing medicationOptimising analgesiaTargeted pharmacological therapy for dysregulation of neuronal activity |
| Haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs vs placebo was administered from intensive care unit admission. | “As a typical antipsychotic drug, haloperidol exerts its action by blocking dopamine D2 receptor.Extensive evidence supported the role of cholinergic deficiency and/or dopaminergic excess as a cause of delirium. In fact, acetylcholine release is regulated by dopaminergic function, i.e., dopamine inhibits the release of acetylcholine by acting at dopamine D2 receptor, whereas blockade of D2 receptor is associated with enhanced release of acetylcholine (and therefore potentially reduced delirium)”17.  | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Melatonin 3 mg before sleep for five consecutive days after surgery.NB: Abbasi et al found no difference in delirium incidence with melatonin compared to control. | “Changes in melatonin concentration influence circadian rhythm and may play an important role in developing delirium”18. | Re-enforcing sleep-wake cycle |
| Eye mask and ear plugs during first post-operative night on ICU.NB: it worked! But impossible to double blind so potential bias! | “Better preservation of sleep quality may promote cognitive function or pain expression. Better sleep leads to a decrease in postoperative disorientation. This result might be the consequence of a lower consumption of morphine in the intervention group, as known adverse effects of opioids are delirium and sedation. Hence the lower opioid consumption by intervention patients may emphasize the increased comfort and benefit related to eye masks and earplugs”19. | Re-enforcing sleep-wake cycleReducing delirium-inducing medication |
| Bright Light Therapy: From Day 2 after surgery, the exposure group underwent two hours of bright light exposure for four days.NB: Ono et al found no significant reduction in incidence of POD (although there was a reduction).  | “Bright light therapy adjusts a persons circadian rhythm. Bright light also has an anxiolytic effect”20. | Re-enforcing sleep-wake cycleAnxiolysis (non-pharmacological) |
| Bright light therapy + Nasal Cannula Oxygen for three days post surgery. | “Some of the protection afforded by Bright Light Therapy on delirium onset may be mediated via effects on the sleep-wake cycle. Outwith its effects on the sleep-wake rhythm and pineal melatonin onset, BLT may impact delirium through other mechanisms, including hormonal systems, photo-immunomodulation and the inflammatory reflex”21. | Re-enforcing sleep-wake cycle.Reducing inflammatory response |
| Bright light therapy: After removal of the endotracheal tube, the study group was exposed to light. The light intensity was about 5000lx immediately before the eyes, and the distance from the light source was about 100 cm. The control group was placed in a natural lighting environment after extubation. | “Manipulation of sleep/wake cycle to restore normal cycle leads to reduction in incidence of POD”22. | Re-enforcing sleep-wake cycle. |
| Combined ropivacaine and dexmedetomidine (0.2% ropivacaine 250 ml and 5 μg/kg dexmedetomidine, at a rate of 5 ml/h or 0.1 mcg/kg/h μg dexmedetomidine vs. only ropivacaine (0.2% ropivacaine, at a rate of 5 ml/h for continuous femoral nerve block as postoperative analgesia after surgery.Wang found: “The incidence of 3-day delirium was lower in dexmedetomidine group (5%) than that in controlled group (15%) (χ2=4.444, *P*<0.05). The difference was statistically significant.” | “Dexmedetomidine combined with ropivacaine for continuous femoral nerve block may improve subjective sleep quality, postoperative analgesia, and reduce delirium in the elderly after total knee arthroplasty”23. | Re-enforcing sleep-wake cycle.Optimising analgesia |
| Low dose dexmedetomidine (continuous infusion at a rate of 0.1 mcg/kg/h) vs placebo for 15 h, i.e., from 5:00 PM on the day of surgery until 8:00 AM on the first day after surgery.NB: Wu et al found no statistically significant difference between the control and exposure groups for POD incidence.  | “Unlike other sedative agents, dexmedetomidine exerts its sedative effects through an endogenous sleep-promoting pathway and preserves sleep architecture to some degree in the preclinical settings”24. | Re-enforcing sleep-wake cycle. |
| 0.5 mg risperidone vs placebo every 12 h by mouth. NB Only those patients who were diagnosed as having subsyndromal delirium at 8h post surgery received the intervention/placebo. Subsyndromal delirium (SSD) has been described in clinical reports as presence of some but not all features of delirium or more definitively as a score of 1–3 on the Intensive Care Delirium Screening Checklist (ICDSC)25. | Antipsychotic.  | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Clonidine 0.5 mcg/kg bolus, followed by continuous infusion at 1-2 mcg/kg/h) or placebo (NaCl 0.9%) in on starting and throughout the weaning period from the mechanical ventilation.NB: Rubino et al found no difference in POD incidence.  | “Studies demonstrated alpha-2 adrenergic agonists, such as clonidine or dexmedetomidine, to have a beneficial effect on neurological recovery and the related weaning from mechanical ventilation in patients developing withdrawal symptoms after interruption of sedation. alpha-2 adrenergic agonists have been suggested to be useful adjuvants to the common postoperative management since they induce sedation and maintain stable systemic blood pressure and low heart rate”26. | Targeted pharmacological therapy for dysregulation of neuronal activity |
| Intravenous dexmedetomidine 0.2 μg/kg/h for 12 hours vs intravenous normal saline for 12 hours27.Guo Found:“The incidence of postoperative delirium, nausea and vomiting in the experimental group was lower than in the control group.” | “postoperative use of dexmedetomidine could still suppress excessive inflammation and the stress response”27. | Optimising analgesiaReducing Inflammatory response. |
| Dexmedetomidine vs propofol at appropriate dose to sedate post operatively28.Huang found no difference in incidence of POD. “No inter-group differences existed in the ICU length of stay and the incidence of delirium” | N/R – The paper was in chinese in full text, but they looked at the pain scores.  | Optimising analgesia |
| Dexmedetomidine (0.1 mcg/kg/h, from intensive care unit admission on the day of surgery) vs placebo for up to 3 days.Xuan found:“Incidence of postoperative delirium was significantly lower in the dexmedetomidine group (30 [13.2%] of 227 patients) than the placebo group (64 [28.3%] of 226 patients (Odds ratio [OR]=0.385, 95% CI 0.238-0.624; p” | “Management of pain and sleep in the elderly is a very important factor in the development of postoperative delirium”29. | Optimising analgesia.Re-enforcing sleep-wake cycle. |
| Dexmeditomidine: after arrival on ICU, 1mcg/kg loading dose, then 0.4 mcg/kg/h during mechanical ventilation; propofol: 5-75 mcg/kg/min during MV after arrival on ICU.Corbett found no difference in incidence of POD.  | “DEX may help with the sleep/wake cycle and therefore prevent incidence of POD”30.  | Re-enforcing sleep-wake cycle. |
| On arrival in the intensive care unit (ICU), patients were assigned randomly to receive either dexmedetomidine (0.2-1.5 mcg/kg/h) or propofol (5-50 mcg/kg/min) with open-label titration to a target Richmond Agitation-Sedation Scale of 0 to -3.NB: POD incidence was a secondary outcome, and 0 patients with DEX had Pod, and 2 patients with propofol had POD.  | “Dexmedetomidine could attenuate inflammatory responses, decrease leukocyte-endothelial interactions, and produce mild hypocoagulation, which could assist in the recruitment of microcirculation. This study demonstrated an increase of small vessels with continuous flow during dexmedetomidine infusion. In addition, studies have shown that propofol infusion for anesthesia reduced capillary blood flow in young patients who underwent transvaginal oocyte retrieval, and changing the sedative infusion from propofol to midazolam resulted in an improvement of the sublingual microcirculation in patients with septic shock. Although propofol, which acts by potentiating gamma aminobutyric acid type-A receptors, also attenuates inflammatory responses, a clinical study showed that the levels of tumor necrosis factor-alpha, interleukin-1, and interleukin-6 were significantly higher in the propofol group than in the dexmedetomidine group during sedation for patients after abdominal surgery. Proinflammatory cytokines induced endothelial-leukocyte cell interactions, resulting in the obstruction of small vessels by leukocyte plugs and the activation of the coagulation system, which may lead to microvascular thrombosis. Cardiac surgery with CPB induced a systemic inflammatory response. In the study presented here, C-reactive protein and the neutrophil-lymphocyte ratio (NLR) tended to be lower in the dexmedetomidine group than that in the propofol group on the morning of the first postoperative day. In addition, the change in NLR from ICU admission to the morning of the first postoperative day was significantly lower in the dexmedetomidine group than in the propofol group. The NLR is an emerging biomarker of inflammation, and elevated NLR predicts a poorer outcome in cardiovascular surgery. Therefore, dexmedetomidine showed stronger inhibitory effects on the inflammatory response than propofol, which may have been one possible reason why changes in the PSVD and De Backer score were significantly greater in the dexmedetomidine group than in the propofol group at T2 (4 hours post surgery)”31. | Optimising analgesia.Reducing inflammatory responseMinimising hypoxaemia.  |
| Dexmedetomidine: Total dose of 3.06 mcg/kg for 10 h during mechanical ventilation upon arrival on ICU; VS midazolam: total dose of 0.34 mg/kg for 11 h during mechanical ventilation upon arrival on ICU32.Wan found a reduction in incidence of POD:“rate of delirium was clearly lower (3.92% vs. 31.63%, P<0.01)” | NR – Full text is in chinese. Analgesia scores were looked at. | Optimising analgesia. |
| Postoperative care in a specialized geriatric ward or a conventional orthopedic ward. The intervention consisted of staff education focusing on the assessment, prevention and treatment of delirium and associated complications. | “A multi-factorial program with systematic assessment, prevention and treatment of complications causing or prolonging delirium, such as urinary tract infections, hypoxemia, anemia, constipation, falls, decubitus ulcers, and nutritional complications, may have contributed both to fewer days with delirium and to shorter hospitalization”33. | Specialist geriatric assessment |
| Ondansetron 8 mg IV or Haloperidol 5 mg IV once34.NB: Both effective. | N/A – not mentioned.  | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Patients were given either 1μg/kg **Dexmedetomidine** (Dexmed group) or 4mg ondansetron (Ondan group) or 5mg haloperidol (Halo group), administered twice daily for 3 consecutive days.Bakri found no difference in incidence between Dexmedetomidine and Haloperidol, suggesting that Dex would make a suitable alternative to Haloperidol as treatment for POD. \*However no statistical significance. But comparison was with Haloperidol a known treatment for POD so good there was no difference. | “Dexmedetomidine has high and specific receptor selectivity; it causes sedation by blocking a single neurotransmitter, norepinephrine, via α2-adrenoceptor bindingwithout disturbing other neurotransmitter systems in particular the cholinergic system.20 The cholinergic neurotransmitter system is linked to cognitive functions including memory, attention, concentration, and learning. Thus, a strong relationship has been documented between drugs with anticholinergic potential and an increased risk of delirium. Dexmedetomidine might attenuate the risk of developing delirium by reducing the use of other GABAergic agents such as benzodiazepines and opiates. Its analgesic effect could reduce the opioid use which may lessen the occurrence of delirium asopioids have been implicated in the development of delirium. More importantly, dexmedetomidine promotes a more physiologic sleep–wake cycle which is very important in the ICU setting”35. | Targeted pharmacological therapy for dysregulation of neuronal activity.Reducing delirium-inducing medicationOptimising analgesia.Re-enforcing sleep-wake cycle. |
| Gabapentin used as add on to treat post-operative pain vs standard care. | “The reduction in delirium appears to be secondary to the opioid-sparing effect of gabapentin”36. | Optimising analgesiaReducing delirium-inducing medication. |
| 5mg of haloperidol intramuscularly vs 5mg of morphine sulfate intramuscularly each given hourly until delirium controlled. | “The authors hypothesized that morphine might be superior to [haloperidol](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/haloperidol) in the initial management of hyperactive [delirium](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/delirium) following cardiac surgery because of its [analgesic](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/anodyne), [anxiolytic](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/anxiolytic), and sedative properties”37. | Optimising analgesia. |
| Dexmedetomidine vs midazolam to wean delirious (POD) patients off mechanical ventilation.Yapici found a reduction in time to extubate with dexmedetomidine, and reduction in delirious state. NB all patients started with POD.  | “Dexmedetomidine induces a sedative response that has properties similar to those of natural sleep. Patients receiving dexmedetomidine experience a clinically effective sedation, yet are easily stilled and uniquely arousable.These benefits may be due to the stimulation of α2 -adrenoreceptors in the central nervous system (specifically in the locus coeruleus). Thus, sympathetic activity is reduced, and norepinephrine release is inhibited”38. | Re-enforcing sleep-wake cycle.Optimising analgesia.Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Postoperative pain management: Either continuous epidural infusion of bupivacaine and fentanyl or continuous intravenous infusion of fentanyl. Infusions were initiated at the first complaint of pain and continued through the 36‐ to 48‐hour stay in the recovery room39.NB: Williams-Russo et al found no difference in POD incidence between the two groups.  | NR – cannot access full text, but looked at pain management. | Optimising analgesia. |
| Postoperative cardiac surgical patients treated with either cimetidine or ranitidine40.NB: Kim et al found no significant difference in Pod incidence between the two groups.  | N/R – Cannot access full text. (Another source: H2-R antagonist. Cimetidine = short acting, Ranitidine = long acting). Both thought to maybe cause delirium, but ranitidine thought better (lower POD incidicence).  | Reducing delirium inducing medication |
| All patients received routine postoperative analgesia; in addition, the treatment group received long-acting oral morphine 30 mg orally twice daily for three days, while the control group received placebo capsules.41NB: Musclow et al found post-operative morphine to increase confusion rather than reduce.  | N/A – was not discussed. Except results demonstrate that opiates could be delirium inducing medications.  | Reducing delirium-inducing medication |

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| **Intervention (PRE-OPERATIVE)** | **Hypothesised Mechanisms of Action** | **Classification of MoA** |
| Intrathecal morphine instead of postoperative intravenous PCA morphine. NB: Beaussier et al did not notice a decrease in delirium in their RCT.  | “Better post-operative pain management may lead to better postoperative recovery in elderly patients”42.  | Optimising analgesia |
| A single 125mg intravenous dose of methylprednisolone preoperatively. | “Steroids reduce neuro-inflammation, which has been suggested as a cause of POD”43. | Reducing inflammatory response |
| Injection with 4 mL/kg 7.5% hypertonic saline vs injection with 4 mL/kg isotonic saline. | “The underlying mechanism may be related to the inhibition of the secretion of inflammatory factors by monocytes. The anti-inflammatory action may form a part of the basis of HS–delirium relationship, and this finding confirms the neuroinflammatory hypothesis of delirium”44. “Hypertonic saline (HS) is widely used as resuscitation fluid in patients with traumatic hemorrhagic shock. HS exerts not only beneficial effects on hemodynamic parameters but also modulatory effects on various immune cell functions, such as degranulation, adhesion, cytokine expression, and reactive oxygen species production. HS modulates local and systemic inflammatory response”44. “Neuroinflammation plays an important role in the development of delirium. Aseptic surgery increases in inflammatory markers in serum and causes inflammation-mediated, hippocampal-dependent, and cognitive dysfunctions. Increased serum levels of inflammatory cytokines postoperatively are associated with memory impairment, reactive microgliosis, and upregulated interleukin (IL)-1β expression in the hippocampus. Inflammatory cytokines are mainly involved in postoperative cognitive delirium [POCD]. Cytokines are categorized as inflammatory cytokines, including IL-1β, IL-6, IL-8, and tumor necrosis factor alpha (TNF-α), and anti-inflammatory cytokines, such as IL-10. Inflammatory cytokines may lead to the occurrence and development of diseases, that is, high levels of inflammatory cytokines are related to the severity of the disease. The role of systemic TNF-α has been widely investigated; a high level of systemic TNF-α is associated with twofold increase in disease symptoms, including apathy, anxiety, depression, and agitation. CD14 + CD16+ monocytes exhibit enhanced capacity for TNF-α generation. Thus, restraining and regulating inflammatory factors may improve the prognosis of delirium”44. | Reducing inflammatory response |
| Pre-operative Comprehensive Geriatric Assessment and optimization vs. usual care. | “Recognition of previously undiagnosed pathology, medication changes, management of anticipated postoperative complications”45. | Specialist geriatric assessment |
| Melatonin 5mg vs. Midazolam 7.5mg vs. Clonidine 100mcg vs. usual care. Drugs were administered twice – once the night before surgery and once 90 minutes prior to surgery. | “Melatonin is naturally produced by the human body and plays an important role in regulation of the sleep-wake cycle. It has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of the hypothalamus. Elderly are more prone to degeneration of these nuclei. This lowers the baseline serum melatonin levels in the elderly individuals. Moreover, surgery induces more lowering of serum melatonin. This produces a state of sleep disorders and disruption of REM sleep postoperatively. Exogenous administration of melatonin is known to facilitate sleep onset and improves quality of sleep. Clinically, it has no amnestic properties and it does not produce impairment of cognitive and psychomotor skills or tests of memory and visual sensitivity”46. | Re-enforcing sleep-wake cycle. |
| Pregabalin 300 mg, administered orally 1 h before surgery vs placebo plus intramuscular 75 mg diclofenac sodium to placebo patients 15-20 minutes before the estimated finishing time of surgery for pain relief after surgery.NB: Akarsu et al found no specific difference in POD between pregabalin and control groups.  | No specific mention of MoA for POD but said this:“Pregabalin can increase the analgesic effects of morphine, nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors. Effective postoperative analgesia prevents many negative impacts of pain; for example it provides a comfortable breathing, reduces the workload of the cardiovascular system, prevents the development of thromboembolic events with early mobilization, and prevents the increase of stress response which happens via neuroendocrine and sympathetic nervous system activation. Studies reported that pregabalin has a significant analgesic effect in acute postoperative pain”47. | Optimising analgesia.  |
| Continuance vs discontinuance of antidepressants in depressed patients 72 hours prior to surgery. | “Withdrawal of antidepressants produces anxiety, agitation and depressed mood”48. | Optimised and Personalised Care. |

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| **Intervention (PERI-OPERATIVE)** | **Hypothesised Mechanisms of Action** | **Classification of MoA** |
| Hospital Elder Life Program (HELP) intervention. | “Early mobilization, Improved sensory stimulation, Improved fluid and nutritional intake, Non-drug sleep improvement, Cognitive activation, and validation improves postoperative recovery”49. | Multi-modal non-pharmacologicalsupport  |
| Modified Hospital Elder Life Program (mHELP) intervention50,51. | “Optimises pain relief, [early mobilization](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/mobilization), and [nutrition](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/nutrition-physiology) (early oral feeding). Combining these approaches reduces the stress response, organ dysfunction, and complications, improving postoperative recovery”50,51. | Optimising analgesiaMulti-modal non-pharmacologicalSupport program |
| Restrictive blood transfusion (Hb < 8 g/dL) vs. liberal blood transfusion (Hb >10 g/dL).NB: Fan et al found no difference between the two transfusion methods in terms of POD incidence. | “Conflicting reports that restrictive blood transfusions have a better postoperative outcome, and other reports stating low blood haemoglobin/oxygenation may lead to postoperative delirium”52.  | Minimising hypoxaemia |
| Comprehensive Geriatric Assessment with postoperative follow- through (Proactive care for older people undergoing surgery - ‘POPS’)53.  | Focused and specialist geriatric care for older surgical patients reduces delirium incidence. | Specialist geriatric assessment |
| Geriatric Liaison Intervention (Pre operative geriatric consultation, individual targeted treatment plan for POD prevention, and daily visits by a geriatric nurse during hospital stay)54.NB: Hempenius et al found no reduction in incidence of POD with this intervention.  | Focused and specialist geriatric care for older surgical patients reduces delirium incidence. | Specialist geriatric assessment |
| Fast-track surgery (FTS) | “FTS prevents upregulation of pro-inflammatory cytokines (e.g. IL-6), reducing the stress response and inflammation”55. | Reducing inflammatory response |
| 1.5mg oral Haloperidol (antipsychotic) administered preoperatively and up to 3 days postoperatively56.NB: Kalisvaart et al found Haliperidol to have no effect on incidence of POD, but found a positive effect on severity and duration of POD.  | Antipsychotic prophylaxis.  | Targeted pharmacological therapy for dysregulation of neuronal activity |
| CareWell in Hospital (CWH) Program57.NB Bakker et al found no significant decrease in delirium incidence.  | NR- Full text not available. | Multi-modal non-pharmacologicalSupport program= Optimised and Personalised Care |
| 10mg total prophylactic oral Olanzapine (antipsychotic) administered (5mg preoperatively and 5mg postoperatively)58. | Antipsychotic prophylaxis. | Targeted pharmacological therapy for dysregulation of neuronal activity |
| Oral Gabapentin 900mg 1-2hrs preoperatively, and 300mg 3x daily for 3 days postoperatively.NB: Leung et al 2017 saw no difference in POD incidence between intervention and control.  | “Intensive pain management postoperatively using an adjuvant agent, gabapentin, would lead to a decrease in the amount of opioids received, a decrease in postoperative pain experienced, thereby resulting in a decrease in the incidence of postoperative delirium”59. | Optimising analgesiaReducing delirium-inducing medication |
| Combined epidural analgesia and general anesthesia followed by postoperative patient-controlled epidural analgesia, using a mixture of 0.125% bupivacaine and sufentanil (PCEA group), or general anesthesia followed by patient controlled anaesthesia with intravenous morphine (PCA group).NB: Mann et al found no difference in incidence of POD between the two groups. Patients reported better analgaesia when using PCEA (epidural) | “Hypothesis that systemically used opioids increase incidence of POD. However, the opioid used here for the PCEA (epidural route) was sufentanil, which is highly lipid soluble and may have a marked systemic effect. Thus a potential reduction in postoperative delirium by trying to prevent the systemic effect of opioids may not be prevented by using the epidural route when using this drug. However, in the PCEA group, Mann et al observed from the fourth postoperative day a more rapid recovery of mental status. This indicates, as suggested by previous that the quality of postoperative analgesia is probably of more importance than is the route of administration or the consumption of opioids in the preservation of cognitive function”60. | Optimising analgesiaReducing delirium-inducing medication |
| “Perioperative Optimisation of Senior Health (POSH) program. The POSH model involves geriatrics experts throughout the perioperative period with specific targeted interventions such as management of comorbidities, reduction of poly-pharmacy, enhancement of mobility and nutrition, and delirium risk mitigation.”NB: Mcdonald et al found not difference in POD incidence when compared with usual care.  | “The POSH model involves geriatrics experts throughout the perioperative period with specific targeted interventions such as management of comorbidities, reduction of poly-pharmacy, enhancement of mobility and nutrition, and delirium risk mitigation”61. | Specialist geriatric assessmentReducing delirium-inducing medication |
| Perioperative continuous airway pressure (CPAP).NB: Nadler et al found no significant difference in POD incidence with CPAP compared to control, however this could be due to lack of adherence with the CPAP-exposed patients.  | “There is an association between obstructive sleep apnoea and the development of acute postoperative delirium. This is likely due to effects of hypoxia. The hypothesis was that CPAP before/during and after surgery would reduce the incidence of POD in patients suffering from obstructive sleep apnoea”62. | Minimising hypoxaemia |
| 3mg melatonin taken orally in the evening for 5 days (from admission to day 5 with surgery usually on day 1 or 2)NB: De Jonghe et al found no difference in incidence/severity/duration of POD with this intervention. | “Disturbances of the circadian sleep–wake cycle represent one of the core features of delirium, leading to the hypothesis that the neurotransmitter melatonin and changes in its metabolism may be involved in the pathogenesis of delirium. Objective measurements have shown that melatonin metabolism is disturbed after abdominal and other types of surgery, insomnia, sleep deprivation and stays in the intensive care unit (ICU), all of which are also known to be factors that contribute to delirium. These characteristics suggest an association between melatonin abnormalities and delirium”63. | Re-enforcing sleep-wake cycle |
| 600mg Gabapentin administered 2 hours pre-operatively, followed by 200mg Gabapentin 3x a day for 4 days postoperatively.NB: Dighe et al found gabapentin had no effect on POD incidence or duration when compared to placebo.  | “Post-operative pain and effects of opioids on the central nervous system are associated with POD. Gabapentin reduces pain and is opioid-sparing so is thought it could maybe reduce POD incidence”64.  | Optimising analgesiaReducing delirium-inducing medication |
| 150 mg pregabalin preoperatively and then 75mg pregabalin twice daily for 7 days post-operatively.NB: Farlinger et al found Pregabalin had no effect on POD incidence, possibly due to patient being given a selective COX2 inhibitor perioperatively which could have nullified pregabalins effects. | “Opioid-sparing effects of pregabalin may decrease POD”65. | Optimising analgesiaReducing delirium-inducing medication |
| 3 doses of 1.5 mg of oral rivastigmine (cholinesterase inhibitor) per day starting the evening before surgery and continuing until the evening of the sixth postoperative day.NB: Gamberini et al found Rivastigmine to have no effect on POD when compared to placebo.  | “Impaired cholinergic transmission is believed to play an important role in the development of delirium”66. | Targeted pharmacological therapy for dysregulation of neuronal activity |
| 0.6 mcg/kg dexmedetomidine for 10 minutes at start of surgery, then 0.4 mcg/kg/h dexmedetomidine until the end of surgery. After surgery, 0.1 mcg/kg/h dexmedetomidine until the end of mechanical ventilation. IV infusion.NB: Li, X et al found no difference in incidence with Dexmedetomidine compared to placebo. | “We hypothesized that use of dexmedetomidine as an anaesthetic adjuvant during cardiac surgery decreased the incidence of delirium, possibly by sparing the consumption of general anaesthetics”67. | Reducing delirium-inducing medication |
| 8 mg Dexamethasone intra-venous before induction of anaesthesia followed by 8 mg dexamethasone every 8h for 3 days. | “Ischaemia-reperfusion damage during certain surgeries can lead to systemic inflammatory response syndrome (SIRS), which is associated with cognitive decline possibly due to the action of enzymes and pro-inflammatory cytokines and reactive oxygen species which can cross the blood brain barrier. Corticosteroids such as dexamethasone have an anti-inflammatory effect and reduce inflammatory events thus reducing incidence of POD. Specifically dexamethasone has a modulatory effect on inflammatory mediators (tissue plasminogen activator, IL-6, IL-8 and TNF-α)”68. | Reducing inflammatory response |
| TJ-54 aka Yokukansan (a traditional Japanese medicine used to treat neurosis, insomnia and irritability and/or agitation in infants) administered 7 days prior to and 4 days post surgery 3 times a day 2.5 mg (7.5mg daily) vs. usual care.NB: Sugano et al found no decrease in incidence of POD with this treatment. However there was less POD with people who already had a prior cognitive impairment.  | “The mechanisms of action of TJ-54 are as follows: i) Partial agonistic effects for 5-HT 1A receptors, ii) antagonistic effects for 5-HT 2A receptors and iii) protective effects against glutamate-induced excitatory neurotoxicity by amelioration of astrocyte dysfunction”69. | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Dexmedetomidine administered at an hourly infusion rate of 0.5 μg/kg for 1 hour before completion of surgery and at 0.2 to 0.7 μg/kg continuously thereafter until the next morning vs placebo.NB: Yang et al found it did not work to reduce incidence of POD.  | “Dexmedetomidine activates α2-adrenergic receptors in the [central nervous system](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/central-nervous-system), inhibits the release of [norepinephrine](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/noradrenalin), and produces sedation, [anxiolysis](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/tranquilizing-activity), and analgesia through net pathways. Another explanation could be related to the sleep characteristics associated with dexmedetomidine. Dexmedetomidine binds to α2 receptors in the [locus ceruleus](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/locus-ceruleus) and inhibits the release of norepinephrine, which is important for NREM sleep”70. | Optimising analgesiaRe-enforcing sleep-wake cycleTargeted pharmacological therapy for dysregulation of neuronal activity |
| Patients were regrouped according to the total Dexmedetomidine dose as placebo (Group 1), low-dose (total dose <8 μg/kg) (Group 2) and high-dose Dex (total dose ≥8 μg/kg) (Group 3) groups over total infusion time period of 24 h. The first group received a placebo, the second group received a 4 mcg/cc concentration of the Dex infusion and the third group received a 8 mcg/cc concentration of the Dex infusion during the procedure. Then all patients received an infusion of Dex at a speed of 0.04 μg/kg/h in the intensive care unit follow-up period71.NB: Balkanay et al didn’t discuss significance in relation to POD. Low incidence of POD across groups. | N/A | Optimising analgesia |
| Loading dose of dexmedetomidine (0.5 µg/kg) after anesthesia induction, followed by 300 µg dexmedetomidine plus 10 mg butorphanol via PCIA during the postoperative period. VS volume-matched infusion of placebo after anesthesia induction, followed by 10 mg butorphanol via PCIA72.NB: Chang et al found no difference between both groups, neither groups developed delirium. | “POD was only looked at as a secondary outcome. Analgesic scores were looked at, as Dexmedetomidine supposedly increased analgesic effect of Butorphanol.” | Optimising analgesia |
| Proactive geriatrics consultation, which began preoperatively or within 24 hours of surgery, vs "usual care." A geriatrician made daily visits for the duration of the hospitalization and made targeted recommendations based on a structured protocol.  | “The clinical judgment of a skilled geriatrician may be helpful in prioritizing among many possible interventions to prevent delirium. In addition, the geriatrician can assist the orthopedics team in the management of other medical issues that may arise during the hospitalization”73. | Specialist geriatric assessment |
| Daily multidisciplinary geriatric intervention VS usual care during hospitalization in the acute phase of hip fracture.A geriatric team that included a geriatrician, a rehabilitation specialist, and a specific social worker also treated patients enrolled in the intervention group74. NB: not clear if it was reduced or not. | N/A – POD a secondary outcome and not specifically mentioned in terms of MoA.  | Specialist geriatric assessment |
| Treatment in an acute geriatric ward or standard orthopedic ward. The key intervention in the acute geriatric ward was Comprehensive Geriatric Assessment including daily interdisciplinary meetings75.NB: Watne et al found no difference in Pod incidence between intervention and control groups.  | N/A – no hypothesis given.  | Specialist geriatric assessment |
| Multidisciplinary inpatient geriatric consultation teams (IGCTs), vs usual care.  | “Multicomponent intervention to prevent delirium is most effective when based on synergistic cooperation between the various healthcare disciplines”76.  | (Multi-modal non-pharmacologicalSupport?)Specialist Geriatric Assessment.= Optimised and Personalised Care. |
| Donepezil (an acetylcholinesterase inhibitor) or placebo for 14 days before surgery and 14 days afterward.NB: Liptzin et al found no difference between the two groups in terms of incidence of POD.  | “Disruption in cholinergic transmission is hypothesized to be a key mechanism in the pathophysiology of delirium”77. | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| Donepezil 5 mg daily or placebo was randomly allocated and initiated within 24 hours of surgery, preoperatively or postoperatively. Daily treatment was continued for 30 days or until side effects or the clinical situation required termination.NB Marcantonio et all so no difference between the intervention and control groups in terms of POD incidence or severity.  | “Cholinesterase inhibitors are commonly used to improve cognitive function in patients with Alzheimer's disease and related dementias by enhancing central cholinergic transmission. Delirium parallels dementia in that an acute deficiency in cholinergic transmission is felt to be a “final common pathway” leading to cognitive dysfunction”78. | Targeted pharmacological therapy for dysregulation of neuronal activity. |
| “Fascia iliaca compartment block (FICB) vs placebo. FICB was administered with a 0.25 mg dose of 0.3 mL/kg bupivacaine on admission and repeated daily every 24 h until delirium occurrence or hip surgery was performed. Twenty-four hours after hip surgery the same dose of FICB was re-administered and repeated daily every 24 h until delirium occurrence or discharge.” | “Recent studies have indicated that unmanaged pain, both acute and chronic, can affect mental status and might precipitate delirium, especially in elderly patients with hip fractures”79. | Optimising analgesia |
| Pre-operative and Post-operative Psychiatric Intervention vs usual care. NB: Schindler et al found no difference in POD incidence between the two groups.  | “More appropriate utilization of pain medications”80. | Optimising analgesia.Optimised and personalised care. |
| 150 mg of Pregabalin before operation and 75 mg of pregabalin twice daily for 5 postoperative days or placebo. | “Gabapentinoids reduce the hyperexcitability of dorsal horn neurones induced by tissue injury and may potentially prevent the development of [chronic pain](https://www-sciencedirect-com.sheffield.idm.oclc.org/topics/medicine-and-dentistry/chronic-pain) after surgery. Our results might indicate that the opioid-sparing effect of pregabalin was linked to a reduction in postoperative confusion on the first postoperative day”81. | Optimising analgesia.Reducing delirium-inducing medication |

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| **Intervention (INTRA-OPERATIVE)** | **Hypothesised Mechanisms of Action** | **Classification of MoA** |
| Ketamine injection.NB Avidan et al did not find this worked to reduce delirium in their RCT.  | “Anti-inflammatory and anti-depressant effects, and increased speed in recovery from general anaesthesia”82.  | Optimising analgesiaReducing inflammatory response |
| Bispectral Index (BIS)-guided anaesthesia.  | “Reduced anaesthetic exposure, and therefore reduced potential long-lasting neurotoxicity due to anaesthetics”83. | Reducing delirium-inducing medication |
| IntraOperative infusion of Dexmedetomidine.NB: Deiner et al found Dexmedetomidine intraoperatively to have no effect on incidence of delirium. Queried whether this was down to timing of administration. | “Dexmedetomidine is an α2-adrenergic agonist with effects that may be beneficial in the postoperative period, including opioid-sparing properties, decreased anesthetic requirements, and neuroprotective effects”84. | Optimising analgesiaReducing delirium-inducing medication |
| Propofol-spinal anaesthesia with spontaneous ventilation using a Laryngeal Mask Airway (LMA)VSPropofol-fentanyl anaesthesia with mechanical ventilation using an endotracheal tube.Kudoh found reduction in POD with the spinal epidural anaesthesia.  | “Propofol is superior to other IV or inhaled anaesthetics due to faster recovery of emergence and faster return of cognition. Furthermore LMA demonstrates faster time to extubation, emergence, and response to commands, possibly decreasing POD”85.  | Reducing delirium-inducing medication |
| Dexmedetomidine 1 mcg/kg bolus followed by 0.2 to 0.7 mcg/kg/h infusion VS dexmedetomidine 1 mcg/kg bolus [diluted to a total volume of 10 mL in saline] VS Saline (control).Lee found a reduction in POD incidence. But also that timing of administration was important. | “Dexmedetomidine significantly reduces levels of IL-6 24 hours after surgery. Cortisol levels are also decreased”86.  | Reducing inflammatory response |
| Anaesthesia plus inhalational agent plus oxygen WITHOUT Nitrous Oxide.NB: Leung et al 2006 did not find that removing N2O from the anaesthesia decreased incidence of POD.  | “There is some evidence that N2O is a cause of POD. N2O may be a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Similar to other NMDA antagonist, N2O has been shown to produce neurotoxic effects in rat brain tissue at high concentrations, and in an age-dependent manner”87. | Reducing delirium-inducing medication |
| Intraoperative infusion of Dexmedetomidine (0.2–0.4 mcg/kg/h continuous infusion)88.Liu found a significant reduction in POD incidence with DEX. | “Dexmedetomidine is neuroprotective for delirium”88.  | Reducing delirium-inducing medication |
| Intra-operative dexmedetomidine, 0.5 lg.kg\_1 bolus followed by 0.4 lg.kg\_1.hr\_1 infusion or placebo.Cheng et al found a significant reduction in POD with Dexmedetomidine compared to control.  | “Dexmedetomidine increases cerebral brain-derived neurotrophic factor concentrations and associated neuroprotective effects. Dexmedetomidine can reverse anaesthesia-induced reductions in plasma concentrations within 24 postoperative hours89.” “Changes in serum concentrations of the brain-derived neurotrophic factor are associated with postoperative delirium89.” | Targeted pharmacological therapy against dysregulation of neuronal Activity |
| Regional (Epidural) Anaesthesia compared to General Anaesthesia. NB: WillamsRusso found no difference in incidence of POD | “General anesthesia has direct pharmacologic effects on the brain. The physiological effects of general and regional anesthesia on cerebral blood flow, oxygen delivery, and cerebral metabolism are markedly different, with regional anaesthesia potentially causing less cognitive complications than general, and therefore potentially reduced incidence in POD”90.  | Reducing delirium-inducing medicationCerebral oxygen metabolism. |
| Propofol Anaesthesia VS Sevoflurane Anaesthesia91.NB: Nishikawa et al found no sig difference between the two, except by day 2/3 post surgery there were less delirium symptoms in those patients anaesthetised with Sevoflurane based.  | N/A.  | Reducing delirium-inducing medication |
| General VS regional Anaesthetic92. NB: Papaiannou found no difference in incidence of POD between the groups | “Endocrine and metabolic changes that occur in this period can be modified by regional techniques.” | Reducing delirium-inducing medication |
| 1mg/kg dexamethasone by intravenous injection once after induction of anaesthesia93.NB: POD incidence was a secondary outcome measure and wasn’t reported on at all in this study.  | N/A: it’s a steroid: Maybe something similar to reducing neuro-inflammation – a potential cause of POD.  | Reducing inflammatory response |
| Intravenous bolus of ketamine (0.5 mg/kg) during anaesthetic induction in the presence of fentanyl and etomidate. | “Ketamine may exert neuroprotective effects, by prevention of excitotoxic injury and apoptosis after cerebral ischaemia, preservation of cerebral perfusion pressure by SNS stimulation, and suppression of inflammatory CNS responses”94.  | Reducing inflammatory response |
| Venously and persistently injected with 7.5 mcg/kg/h nimodipine prior to induction of anaesthesia until first incision. | “The reduction of brain injury and improvement of cerebral oxygen metabolism may be involved in the mechanism. Nimodipine, can expand the cerebral blood vessels, improve the cerebral circulation, and protect the brain. Nimodipine is a clinical commonly used calcium antagonist, which can lower the apoptosis rate of hippocampal neuron to reduce the incidence of postoperative cognitive dysfunction (POCD)”95. | Improving cerebral oxygen metabolismReducing inflammatory responseTargeted pharmacological … |
| Bolus of dexmedetomidine at 0.8-1.0 mcg/kg followed by 0.1-0.5mcg/kg/h infusion vs propofol96.Mei found a lower incidence in POD in those treated with DEX. | NR – Full text not found.Thought to be good as supplementary to peripheral nerve block. | Reducing delirium-inducing medication |
| 250 mg methylprednisolone at anaesthetic induction and 250 mg methylprednisolone before cardiopulmonary bypass97.NB: Royse et al found no reduction in incidence of POD.  | Not clear from paper, but Methylprednisolone is a steroid with anti-inflammatory effects.  | Reducing inflammatory response |
| The dexmedetomidine group received a bolus dose of dexmedetomidine (1 μg/kg diluted in 100 ml of normal saline over 10 min), followed by infusion (0.2–0.6 μg/kg/h). The propofol group received a propofol infusion at the rate of 0.25–1 mg/kg/hSheikh found: risk of delirium was significantly less with DEX. Reduced incidence in POD.  | “Several studies consider this benefit to be related to the gamma-aminobutyric acid receptor-sparing activity, minimal respiratory depression, normal sleep-mimicking effect, lack of anticholinergic activity, and the opioid-sparing effect”98. | Reducing delirium-inducing medicationOptimising analgesia.Re-enforcing sleep-wake cycle.  |
| Methylprednisolone (250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass) vs placebo.NB: Whitlock et al found this did not work.  | “Cardiopulmonary bypass initiates a systemic inflammatory response syndrome that is associated with postoperative morbidity and mortality. Steroids suppress inflammatory responses and might improve outcomes in patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass”99. | Reducing inflammatory response |
| BIS-guided (bi-spectral index data guided) anaesthesia (i.e. EEG monitoring of depth of anaesthesia) vs. usual care. | “Reducing episodes of extremely deep anaesthesia reduces the neurotoxic effects of anaesthesia thus reducing the incidence of POD”100. | Reducing delirium-inducing medication. |
| Variable ventilation vs. conventional ventilation during surgery. | “By reducing the systemic proinflammatory response. In recent years, a growing amount of evidence suggested that increased inflammatory response and excessive release of proinflammatory cytokines such as IL-6 and TNF-α, were associated with postoperative cognitive impairment. The values of pre- and postoperative inflammatory cytokines including IL-6, IL-8 and TNF-α were compared between the two groups. The levels of these inflammatory cytokines were all significantly higher in CV (conventional ventilation) group than those in VV (variable ventilation) group on the 1st postoperative day (P<0.05). On 7th postoperative day, the levels of cytokines decreased significantly both in two groups. However, the levels of IL-6 and TNF-α in CV group remained much higher compared with VV group, which was consistent with a higher degree of inflammatory stress response in the CV group”101. | Reducing inflammatory response |
| Patients were allocated to receive either propofol or desflurane as the primary anaesthetic agent for the duration of surgery.NB: Royse et al found higher incidence of POD with propofol, but found reduced POD with desflurane | “Different classes of anaesthetic could affect the development of postoperative cognitive dysfunction”102. | Reducing delirium-inducing medication. |
| Dexamethasone 1 mg/kg or placebo at the induction of anesthesia.NB: Sauer et al found no decrease in incidence of POD.  | “Surgery and the use of cardiopulmonary bypass can trigger a systemic inflammatory response. We hypothesized that intraoperative administration of high-dose dexamethasone, a drug with potent anti-inflammatory effects, would reduce the incidence of delirium”103. | Reducing inflammatory response |
| 0.5mcg/kg dexmedetomidine initially for 10 mins at start of surgery followed by maintenance at 0.4 mcg/kg until end of surgery vs IV injection of 0.03mg/kg midazolam vs saline.He found a reduction in incidence of POD with DEX.  | “First, DEX can bind to the spinal cord, brain and other norepinephrine receptors in the whole body and studies have revealed that changes in the noradrenergic system may be associated with POD in patients. Second, studies have manifested that application of opioids or other general anesthetics increases the incidence rate of POD, while the existing studies have indicated that DEX can reduce the dosage of opioids so as to prevent opioid-induced POD. Third, propofol and benzodiazepines such as midazolam have a high affinity to γ-aminobutyric acid receptor, and changes in γ-aminobutyric acid receptors result in a variety of neurotransmitter changes, thus leading to the occurrence of POD. Studies have confirmed that the affinity of DEX to γ-aminobutyric acid receptors decreases, and the binding also declines. Fourth, some scholars hold that delirium was an acute stress reaction, and operation and trauma can rapidly increase the blood cortisol level. Many studies have evidenced that the elevation of cortisol concentration after the stimulation can increase the incidence rate of POD, while DEX can reduce hemodynamic changes during anesthesia and operations and the stress response. Fifth, it has been reported that DEX has certain neuroprotective effects, probably through the regulation of pro-apoptotic and anti-apoptotic proteins. Finally, DEX has a strong anti-inflammatory effect, and studies have demonstrated that cytokines such as interleukins, tumor necrosis factors and interferons can cause POD by increasing blood-brain barrier permeability and altering the delivery of neurotransmitters”104. | Targeted pharmacological therapy for dysregulation of neuronal activity.Optimising analgesia.Reducing delirium-inducing medication.Reducing inflammatory response |
| I.v. injection ketamine 0.5 mg/kg vs. i.v. injection dexmedetomidine 1 mcg/kg before induction of anesthesia followed by continuous infusion at 0.5 mcg/kg/h till 30 min before the end of surgery vs both 0.5 mg/kg ketamine and 1.0 mcg/kg/h dexmedetomidine over 10 min by intravenous injection followed by a continuous infusion of dexmedetomidine at 0.5 mcg/kg/h till 30 min before the end of surgery vs saline control.Ma found a decrease in incidence of POD with this intervention. This was significant. | “Applied together dexmedetomidine could alleviate the side effects of ketamine, and also has the anti-inflammatory effects”105.  | Optimising analgesia.Reducing delirium-inducing medication.Reducing inflammatory response |
| Intravenous injection of Dexmedetomidine and then intravenous injection of 0.2-0.7 mcg/kg/h Dexmedetomidine to maintain anesthesia. vs intravenous injection of 0.05 mcg/kg/h Midazolam Maleate and then intravenous injection of 0.02-0.08 mcg/kg/h Midazolam Maleate to maintain anesthesia.Yu found a decrease in occurrence of POD with DEX. Significant result.  | “Postoperative delirium may have positive correlation with anesthesia-induced vasodilation function and hypermetabolic inflammatory status. Furthermore, it is also related to the severity of surgical trauma. As an imidazole derivative, Dexmedetomidine is of high selectivity, and its action position is blue patch nucleus. Through excitation and by using presynaptic membrane A2 receptor, Dexmedetomidine can inhibit the release of noradrenaline and terminate pain signal transduction. It can also stabilize hemodynamics, reduce the dosages of general anesthesia and analgesic drugs, and relieve cardiovascular stress reaction with light respiratory depression. Dexmedetomidine had low affinity to γ- aminobutyric acid receptor in the central nervous system, which reduced the occurrence of postoperative delirium while exerting analgesic and sedative effects”106. | Reducing inflammatory response.Optimising analgesia.Reducing delirium-inducing medication. |
| AEP-guided anaesthesia: Depth of anaesthesia aimed at an auditory evoked potential AEP index (AAI) between 15 and 25 vs control where depth of anaesthesia was guided by clinical signs.Anesthesia was guided by auditory evoked potential AEP (AAI between 15 and 25 was regarded as adequate) vs control where depth of anaesthesia was guided by clinical signs. | “The greater the anaesthetic concentration, the greater appears to be the cognitive decline during the first 24 h because AEP-guided anaesthesia resulted in a lower incidence of cognitive impairment compared to clinically guided anaesthesia”107.“AEP-guided anesthesia allowed us to reduce anesthetic depth and doses of anesthesia drugs”108. | Reducing delirium-inducing medication. |
| Intraoperative Bispectral Index (BIS)-guided vs end-tidal anesthetic concentration-guided depth of anesthesia protocols.NB: Whitlock et al found a decrease in POD incidence but not significant.  | “One hypothesis is that electroencephalogram (EEG) or BIS guidance leads to avoidance or minimization of periods of EEG burst suppression or persistent suppression. These EEG patterns are not seen during physiological sleep and have been associated with adverse outcomes in ICU patients”109. | Re-enforcing sleep-wake cycle.  |
| Dexmedetomidine 1.0 μg/kg intravenously at 10 min before routine anesthesia induction, then injected with 0.5 μg/kg/h till surgery finished.Shu found that the POD score was significantly lower with DEX than the Control.  | “Dexmedetomidine may reduce cerebral oxygen consumption by reducing cerebral oxygen metabolism, and further improve brain oxygenation and the hypoxia tolerance of brain tissue, to play a protective effect on cerebral tissues.Can prevent brain damage, possibly achieved by inhibiting the inflammatory response”110. | Minimising hypoxaemia.Improving cerebral oxygen metabolism.Reducing inflammatory response |
| Halothane vs Epidural anaesthesia.NB: Berggren et al found no difference between the two groups.  | “Post-operative hypoxaemia may lead to delirium”111. | Minimising hypoxaemia. |
| Intravenous anesthesia (TIVA) with propofol vs inhalation anesthesia with isofluraneNB: Cai et al found that inhalation anaesthesia lead to more POCD.  | “We hypothesize that there is an association between the ApoE ε4 allele and postoperative cognitive dysfunction in patients undergoing general anesthesia. TIVA more suitable for elderly patients especially if carrying the ApoE E4 allele”112. | Reducing delirium-inducing medication. |
| Propofol Sedation depth was titrated using processed electroencephalography with the bispectral index (BIS), and patients were randomized to receive either deep (BIS, approximately 50) or light (BIS, >or=80) sedation. | “Some drug-induced alteration in brain activity as the mechanism for the increased prevalence of postoperative delirium in the deep sedation group”113. | Reducing delirium-inducing medication. |
| General vs Regional anesthesia.NB: Slor et al found no difference in POD incidence between the two groups.  | “Older adults are likely to be more sensitive to adverse side effects of certain anesthetics and analgesics than younger individuals. The greater sensitivity is thought to be causally related to the decrease in cholinergic activity that accompanies the physiological changes of the body in normal aging. An imbalance in acetylcholine-mediated neural systems has been associated with delirium”114. | Reducing delirium-inducing medication.Targeted pharmacological therapy for dysregulation of neuronal activity |
| Epidural anaesthesia: The patients were randomly assigned to one of two levels of intraoperative mean arterial blood pressure management: either to a markedly hypotensive mean arterial blood pressure range of 45–55 mmHg or to a less hypotensive range of 55–70 mmHg115.NB: Williams-Russo et al found no sig difference between the two groups for POD incidence. | N/A – did not discuss this as a prevention of delirium, really only to check that hypotensive MABP doesn’t cause delirium postoperatively. | Minimising hypoxaemia.  |

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Supplementary Material 6

Supplementary Material 6

**hMOA and intervention**

|  |
| --- |
| **PRE-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Optimised and Personalised Care | Comprehensive Geriatric Assessment[1]. |
| Continuance of Anti-depressant Treatment[2]. |
| Re-enforcing Sleep-Wake Cycle | Melatonin[3]. |
| Reducing Inflammatory Response | Methylprednisolone[4]. |
| Hypertonic Saline injection[5]. |
| Optimising Analgesia | Intrathecal Morphine[6]. |
| Pregabalin[7]. |
| Targetting neuronal dysregulation | Rivastigmine[8] |

***A6.T1:*** *Demonstrating intervention by proposed mechanism of action of intervention group for pre-operative interventions.*

|  |
| --- |
| **INTRA-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Re-enforcing Sleep-Wake Cycle | Bispectral Index (BIS)-guided Anaesthesia[9]. |
| Dexmedetomidine[10]. |
| Reducing Inflammatory Response | Variable Ventilation[11]. |
| Ketamine[12, 13]. |
| Dexmedetomidine[14–17]. |
| Ketamine and Dexmedetomidine[18]. |
| Dexamethasone[19, 20]. |
| Methylprednisolone[21, 22]. |
| Nimodipine[23].  |
| Optimising Analgesia | Ketamine[12]. |
| Dexmedetomidine[10, 15, 16, 24]. |
| Ketamine and Dexmedetomidine[18]. |
| Minimising Hypoxaemia | Regional (Epidural) Anaesthesia[25]. |
| Mean Arterial Blood Pressure Management[26]. |
| Dexmedetomidine[17]. |
| Improving Cerebral Oxygen Metabolism | Regional (Epidural) Anaesthesia[27]. |
| Dexmedetomidine[17]. |
| Nimodipine[23].  |
| Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity | Regional (Epidural) Anaesthesia[28]. |
| Dexmedetomidine[15, 29]. |
| Nimodipine[23]. |
| Reducing Delirium-inducing Medication | Bispectral Index (BIS)-guided Anaesthesia[30, 31]. |
| Light Bispectral Index (BIS)-guided Anaesthesia[32].  |
| Auditory Evoked Potential (AEP)-guided Anaesthesia[33, 34]. |
| Anaesthesia + inhalation agent + O2 without Nitrous Oxide[35]. |
| Propofol-Spinal Anaesthesia (Regional) with Spontaneous Ventilation using a Laryngeal Mask Airway (LMA)[36]. |
| Desflurane as Primary Anaesthetic Agent[37]. |
| Sevoflurane as Primary Anaesthetic Agent[38]. |
| Total Intravenous Anaesthesia (TIVA)[39]. |
| Regional (Epidural) Anaesthesia[27, 28, 40]. |
| Dexmedetomidine[10, 15, 16, 24, 41, 42]. |
| Ketamine and Dexmedetomidine[18]. |

***A6.T2:*** *Demonstrating intervention by proposed mechanism of action of intervention group for intra-operative interventions.*

|  |
| --- |
| **POST-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Optimised and Personalised Care | Post-operative Care in a Specialised Geriatric Ward[43]. |
| Anxiolysis (Non-Pharmalogical) | Music Therapy[44]. |
| Bright Light Therapy[45]. |
| Re-enforcing Sleep-Wake Cycle | Eye Mask and Ear Plugs[46]. |
| Bright Light Therapy[45, 47, 48]. |
| Melatonin[49]. |
| L-Tryptophan[50]. |
| Intramuscular Diazepam, and Continuous Intravenous Flunitrazepam and Pethidine[51]. |
| Haloperidol[52]. |
| Dexmedetomidine[53–60]. |
| Dexmedetomidine and Ropivacaine[61]. |
| Reducing Inflammatory Response | Bright Light Therapy[47]. |
| Dexmedetomidine[53, 62, 63]. |
| Optimising Analgesia | Continuous Epidural Infusion of Bupivacaine and Fentanyl[64]. |
| Intramuscular Morphine Sulfate[65]. |
| Gabapentin[66]. |
| Parecoxib[67]. |
| Dexmedetomidine[53, 54, 70–72, 56, 58–60, 62, 63, 68, 69]. |
| Dexmedetomidine and Ropivacaine[61]. |
| Minimising Hypoxaemia | Dexmedetomidine[62]. |
| Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity | L-Tryptophan[50]. |
| Donepezil[73]. |
| Cyproheptadine[74]. |
| Risperidone[75, 76]. |
| Haloperidol[52, 77–79]. |
| Ondansetron[79, 80]. |
| Clonidine[81]. |
| Dexmedetomidine[58–60, 69, 70]. |
| Reducing Delirium-inducing Medication | Eye Mask and Ear Plugs[46]. |
| Post-operative Analgesia Without Long-Acting Morphine[82]. |
| Ranitidine or Cimetidine[83].  |
| Parecoxib[67]. |
| Gabapentin[66]. |
| Dexmedetomidine[53, 54, 58, 60, 69, 70]. |

***A6.T3:*** *Demonstrating intervention by proposed mechanism of action of intervention group for post-operative interventions.*

|  |
| --- |
| **PERI-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Optimised and Personalised Care | Comprehensive Geriatric Assessment (CGA) and Geriatric Follow-through[84–86]. |
| Daily Geriatric Care[87–91]. |
| Multidisciplinary Geriatric Care[86, 92–94]. |
| Psychotherapy[95]. |
| Management of Co-morbidities[94]. |
| Enhancement of Mobility and Nutrition[86, 87, 90, 91, 94]. |
| Sensory Stimulation (e.g. Visual Aids, Hearing Aids, Personal Items)[87]. |
| Cognitive Stimulation[86, 87, 90, 91]. |
| Re-enforcing Sleep-Wake Cycle | Sleep Support[87]. |
| Melatonin[96]. |
| Dexmedetomidine[97]. |
| Reducing Inflammatory Response | Fast-track Surgery[98]. |
| Dexamethasone[99]. |
| Optimising Analgesia | Psychotherapy[95]. |
| Combined Epidural Analgesia and General Anaesthetic with Patient-controlled Post-operative Epidural Analgesia (Bupivacaine and Sufentanil)[100]. |
| Fascia Iliaca Compartment Block[101]. |
| Gabapentin[102, 103]. |
| Pregabalin[104, 105]. |
| Dexmedetomidine[97, 106, 107]. |
| Minimising Hypoxaemia | Continuous Positive Airway Pressure (CPAP)[108]. |
| Liberal Blood Transfusion[109]. |
| Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity | TJ-54 (Yokukansan)[110]. |
| Donepezil [111, 112]. |
| Rivastigmine[113]. |
| Haloperidol[114]. |
| Olanzapine[115]. |
| Dexmedetomidine[97]. |
| Reducing Delirium-Inducing Medication | Medication Review/Preventing Polypharmacy[86, 94]. |
| Combined Epidural Analgesia and General Anaesthetic with Patient-controlled Post-operative Epidural Analgesia (Bupivacaine and Sufentanil)[100]. |
| Gabapentin[102, 103]. |
| Pregabalin[104, 105]. |
| Dexmedetomidine[116]. |

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***A6.T4:*** *Demonstrating intervention by proposed mechanism of action of intervention group for peri-operative interventions.*

Mechanism and timing

**A**

|  |
| --- |
| **Reducing Delirium Inducing Medication** |
| Total Number of Studies: 39 |
| PRE: 0 | INTRA: 20 | POST: 11 | PERI: 8 |
| Number of Interventions: 19 |
| PRE: 0 | INTRA: 11 | POST: 6 | PERI: 5 |
| Pharmacological: 17 |
| Non-pharmacological: 2 |

**B**

|  |
| --- |
| **Optimising Analgesia** |
| Total Number of Studies: 36 |
| PRE: 2 | INTRA: 6 | POST: 18 | PERI: 10 |
| Number of Interventions: 13 |
| PRE: 2 | INTRA: 3 | POST: 6 | PERI: 6 |
| Pharmacological: 12 |
| Non-pharmacological: 1 |

**C**

|  |
| --- |
| **Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity** |
| Total Number of Studies: 29 |
| PRE: 1 | INTRA: 4 | POST: 17 | PERI: 7 |
| Number of Interventions: |
| PRE: 1 | INTRA: 4 | POST: 8 | PERI: 6 |
| Pharmacological: 14 |
| Non-pharmacological: 0 |

**D**

|  |
| --- |
| **Re-enforcing Sleep-wake Cycle** |
| Total Number of Studies: 23 |
| PRE: 1 | INTRA: 2 | POST: 17 | PERI: 3 |
| Number of Interventions: 10 |
| PRE: 1 | INTRA: 2 | POST: 8 | PERI: 3 |
| Pharmacological: 7 |
| Non-pharmacological: 3 |

**E**

|  |
| --- |
| **Reducing Inflammatory Response** |
| Total Number of Studies: 21 |
| PRE: 2 | INTRA: 13 | POST: 4 | PERI: 2 |
| Number of Interventions: 10 |
| PRE: 2 | INTRA: 7 | POST: 2  | PERI: 2 |
| Pharmacological: 7 |
| Non-pharmacological: 3 |

**F**

|  |
| --- |
| **Optimised and Personalised Care** |
| Total Number of Studies: 15 |
| PRE: 2 | INTRA: 0 | POST: 1 | PERI: 12 |
| Number of Interventions: 10 |
| PRE: 2 | INTRA: 0 | POST: 1 | PERI: 8 |
| Pharmacological: 1 |
| Non-pharmacological: 9 |

**G**

|  |
| --- |
| **Minimising Hypoxaemia** |
| Total Number of Studies: 6 |
| PRE: 0 | INTRA: 3 | POST: 1 | PERI: 2 |
| Number of Interventions: 5 |
| PRE: 0 | INTRA: 3 | POST: 1 | PERI: 2 |
| Pharmacological: 3 |
| Non-pharmacological: 2 |

**H**

|  |
| --- |
| **Improving Cerebral Oxygen Metabolism** |
| Total Number of Studies: 3 |
| PRE: 0 | INTRA: 3 | POST: 0 | PERI: 0 |
| Number of Interventions: 3 |
| PRE: 0 | INTRA: 3 | POST: 0 | PERI: 0 |
| Pharmacological: 3 |
| Non-pharmacological: 0 |

**I**

|  |
| --- |
| **Anxiolysis (Non-pharmacological)** |
| Total Number of Studies: 2 |
| PRE: 0 | INTRA: 0 | POST: 2 | PERI: 0 |
| Number of Interventions: 2 |
| PRE: 0 | INTRA: 0 | POST: 2 | PERI: 0 |
| Pharmacological: 0 |
| Non-pharmacological: 2 |

*Supplementary Material 6: Tables showing hypothesised mechanisms of action by number of studies and interventions, stratified according to timing relative to surgery, together with the number of interventions that were either pharmacological or non-pharmacological. A) Reducing delirium inducing medication; B) Optimising analgesia; C) Targeted pharmacological therapy against dysregulation of neuronal activity; D) Re-enforcing sleep-wake cycle; E) Reducing inflammatory response; F) Optimised and personalised care; G) Minimising Hypoxaemia; H) Improving cerebral oxygen metabolism; I) Anxiolysis (non-pharmacological).*

**hMOA and intervention**

|  |
| --- |
| **PRE-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Optimised and Personalised Care | Comprehensive Geriatric Assessment[1]. |
| Continuance of Anti-depressant Treatment[2]. |
| Re-enforcing Sleep-Wake Cycle | Melatonin[3]. |
| Reducing Inflammatory Response | Methylprednisolone[4]. |
| Hypertonic Saline injection[5]. |
| Optimising Analgesia | Intrathecal Morphine[6]. |
| Pregabalin[7]. |
| Targetting neuronal dysregulation | Rivastigmine[8] |

***A6.T1:*** *Demonstrating intervention by proposed mechanism of action of intervention group for pre-operative interventions.*

|  |
| --- |
| **INTRA-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Re-enforcing Sleep-Wake Cycle | Bispectral Index (BIS)-guided Anaesthesia[9]. |
| Dexmedetomidine[10]. |
| Reducing Inflammatory Response | Variable Ventilation[11]. |
| Ketamine[12, 13]. |
| Dexmedetomidine[14–17]. |
| Ketamine and Dexmedetomidine[18]. |
| Dexamethasone[19, 20]. |
| Methylprednisolone[21, 22]. |
| Nimodipine[23].  |
| Optimising Analgesia | Ketamine[12]. |
| Dexmedetomidine[10, 15, 16, 24]. |
| Ketamine and Dexmedetomidine[18]. |
| Minimising Hypoxaemia | Regional (Epidural) Anaesthesia[25]. |
| Mean Arterial Blood Pressure Management[26]. |
| Dexmedetomidine[17]. |
| Improving Cerebral Oxygen Metabolism | Regional (Epidural) Anaesthesia[27]. |
| Dexmedetomidine[17]. |
| Nimodipine[23].  |
| Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity | Regional (Epidural) Anaesthesia[28]. |
| Dexmedetomidine[15, 29]. |
| Nimodipine[23]. |
| Reducing Delirium-inducing Medication | Bispectral Index (BIS)-guided Anaesthesia[30, 31]. |
| Light Bispectral Index (BIS)-guided Anaesthesia[32].  |
| Auditory Evoked Potential (AEP)-guided Anaesthesia[33, 34]. |
| Anaesthesia + inhalation agent + O2 without Nitrous Oxide[35]. |
| Propofol-Spinal Anaesthesia (Regional) with Spontaneous Ventilation using a Laryngeal Mask Airway (LMA)[36]. |
| Desflurane as Primary Anaesthetic Agent[37]. |
| Sevoflurane as Primary Anaesthetic Agent[38]. |
| Total Intravenous Anaesthesia (TIVA)[39]. |
| Regional (Epidural) Anaesthesia[27, 28, 40]. |
| Dexmedetomidine[10, 15, 16, 24, 41, 42]. |
| Ketamine and Dexmedetomidine[18]. |

***A6.T2:*** *Demonstrating intervention by proposed mechanism of action of intervention group for intra-operative interventions.*

|  |
| --- |
| **POST-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Optimised and Personalised Care | Post-operative Care in a Specialised Geriatric Ward[43]. |
| Anxiolysis (Non-Pharmalogical) | Music Therapy[44]. |
| Bright Light Therapy[45]. |
| Re-enforcing Sleep-Wake Cycle | Eye Mask and Ear Plugs[46]. |
| Bright Light Therapy[45, 47, 48]. |
| Melatonin[49]. |
| L-Tryptophan[50]. |
| Intramuscular Diazepam, and Continuous Intravenous Flunitrazepam and Pethidine[51]. |
| Haloperidol[52]. |
| Dexmedetomidine[53–60]. |
| Dexmedetomidine and Ropivacaine[61]. |
| Reducing Inflammatory Response | Bright Light Therapy[47]. |
| Dexmedetomidine[53, 62, 63]. |
| Optimising Analgesia | Continuous Epidural Infusion of Bupivacaine and Fentanyl[64]. |
| Intramuscular Morphine Sulfate[65]. |
| Gabapentin[66]. |
| Parecoxib[67]. |
| Dexmedetomidine[53, 54, 70–72, 56, 58–60, 62, 63, 68, 69]. |
| Dexmedetomidine and Ropivacaine[61]. |
| Minimising Hypoxaemia | Dexmedetomidine[62]. |
| Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity | L-Tryptophan[50]. |
| Donepezil[73]. |
| Cyproheptadine[74]. |
| Risperidone[75, 76]. |
| Haloperidol[52, 77–79]. |
| Ondansetron[79, 80]. |
| Clonidine[81]. |
| Dexmedetomidine[58–60, 69, 70]. |
| Reducing Delirium-inducing Medication | Eye Mask and Ear Plugs[46]. |
| Post-operative Analgesia Without Long-Acting Morphine[82]. |
| Ranitidine or Cimetidine[83].  |
| Parecoxib[67]. |
| Gabapentin[66]. |
| Dexmedetomidine[53, 54, 58, 60, 69, 70]. |

***A6.T3:*** *Demonstrating intervention by proposed mechanism of action of intervention group for post-operative interventions.*

|  |
| --- |
| **PERI-OPERATIVE** |
| **Hypothesised Mechanism of Action** | **Intervention** |
| Optimised and Personalised Care | Comprehensive Geriatric Assessment (CGA) and Geriatric Follow-through[84–86]. |
| Daily Geriatric Care[87–91]. |
| Multidisciplinary Geriatric Care[86, 92–94]. |
| Psychotherapy[95]. |
| Management of Co-morbidities[94]. |
| Enhancement of Mobility and Nutrition[86, 87, 90, 91, 94]. |
| Sensory Stimulation (e.g. Visual Aids, Hearing Aids, Personal Items)[87]. |
| Cognitive Stimulation[86, 87, 90, 91]. |
| Re-enforcing Sleep-Wake Cycle | Sleep Support[87]. |
| Melatonin[96]. |
| Dexmedetomidine[97]. |
| Reducing Inflammatory Response | Fast-track Surgery[98]. |
| Dexamethasone[99]. |
| Optimising Analgesia | Psychotherapy[95]. |
| Combined Epidural Analgesia and General Anaesthetic with Patient-controlled Post-operative Epidural Analgesia (Bupivacaine and Sufentanil)[100]. |
| Fascia Iliaca Compartment Block[101]. |
| Gabapentin[102, 103]. |
| Pregabalin[104, 105]. |
| Dexmedetomidine[97, 106, 107]. |
| Minimising Hypoxaemia | Continuous Positive Airway Pressure (CPAP)[108]. |
| Liberal Blood Transfusion[109]. |
| Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity | TJ-54 (Yokukansan)[110]. |
| Donepezil [111, 112]. |
| Rivastigmine[113]. |
| Haloperidol[114]. |
| Olanzapine[115]. |
| Dexmedetomidine[97]. |
| Reducing Delirium-Inducing Medication | Medication Review/Preventing Polypharmacy[86, 94]. |
| Combined Epidural Analgesia and General Anaesthetic with Patient-controlled Post-operative Epidural Analgesia (Bupivacaine and Sufentanil)[100]. |
| Gabapentin[102, 103]. |
| Pregabalin[104, 105]. |
| Dexmedetomidine[116]. |

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***A6.T4:*** *Demonstrating intervention by proposed mechanism of action of intervention group for peri-operative interventions.*

Mechanism and timing

**A**

|  |
| --- |
| **Reducing Delirium Inducing Medication** |
| Total Number of Studies: 39 |
| PRE: 0 | INTRA: 20 | POST: 11 | PERI: 8 |
| Number of Interventions: 19 |
| PRE: 0 | INTRA: 11 | POST: 6 | PERI: 5 |
| Pharmacological: 17 |
| Non-pharmacological: 2 |

**B**

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| --- |
| **Optimising Analgesia** |
| Total Number of Studies: 36 |
| PRE: 2 | INTRA: 6 | POST: 18 | PERI: 10 |
| Number of Interventions: 13 |
| PRE: 2 | INTRA: 3 | POST: 6 | PERI: 6 |
| Pharmacological: 12 |
| Non-pharmacological: 1 |

**C**

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| --- |
| **Targeted Pharmacological Therapy Against Dysregulation of Neuronal Activity** |
| Total Number of Studies: 29 |
| PRE: 1 | INTRA: 4 | POST: 17 | PERI: 7 |
| Number of Interventions: |
| PRE: 1 | INTRA: 4 | POST: 8 | PERI: 6 |
| Pharmacological: 14 |
| Non-pharmacological: 0 |

**D**

|  |
| --- |
| **Re-enforcing Sleep-wake Cycle** |
| Total Number of Studies: 23 |
| PRE: 1 | INTRA: 2 | POST: 17 | PERI: 3 |
| Number of Interventions: 10 |
| PRE: 1 | INTRA: 2 | POST: 8 | PERI: 3 |
| Pharmacological: 7 |
| Non-pharmacological: 3 |

**E**

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| --- |
| **Reducing Inflammatory Response** |
| Total Number of Studies: 21 |
| PRE: 2 | INTRA: 13 | POST: 4 | PERI: 2 |
| Number of Interventions: 10 |
| PRE: 2 | INTRA: 7 | POST: 2  | PERI: 2 |
| Pharmacological: 7 |
| Non-pharmacological: 3 |

**F**

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| --- |
| **Optimised and Personalised Care** |
| Total Number of Studies: 15 |
| PRE: 2 | INTRA: 0 | POST: 1 | PERI: 12 |
| Number of Interventions: 10 |
| PRE: 2 | INTRA: 0 | POST: 1 | PERI: 8 |
| Pharmacological: 1 |
| Non-pharmacological: 9 |

**G**

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| **Minimising Hypoxaemia** |
| Total Number of Studies: 6 |
| PRE: 0 | INTRA: 3 | POST: 1 | PERI: 2 |
| Number of Interventions: 5 |
| PRE: 0 | INTRA: 3 | POST: 1 | PERI: 2 |
| Pharmacological: 3 |
| Non-pharmacological: 2 |

**H**

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| --- |
| **Improving Cerebral Oxygen Metabolism** |
| Total Number of Studies: 3 |
| PRE: 0 | INTRA: 3 | POST: 0 | PERI: 0 |
| Number of Interventions: 3 |
| PRE: 0 | INTRA: 3 | POST: 0 | PERI: 0 |
| Pharmacological: 3 |
| Non-pharmacological: 0 |

**I**

|  |
| --- |
| **Anxiolysis (Non-pharmacological)** |
| Total Number of Studies: 2 |
| PRE: 0 | INTRA: 0 | POST: 2 | PERI: 0 |
| Number of Interventions: 2 |
| PRE: 0 | INTRA: 0 | POST: 2 | PERI: 0 |
| Pharmacological: 0 |
| Non-pharmacological: 2 |

*Supplementary Material 6: Tables showing hypothesised mechanisms of action by number of studies and interventions, stratified according to timing relative to surgery, together with the number of interventions that were either pharmacological or non-pharmacological. A) Reducing delirium inducing medication; B) Optimising analgesia; C) Targeted pharmacological therapy against dysregulation of neuronal activity; D) Re-enforcing sleep-wake cycle; E) Reducing inflammatory response; F) Optimised and personalised care; G) Minimising Hypoxaemia; H) Improving cerebral oxygen metabolism; I) Anxiolysis (non-pharmacological).*

**Supplementary Material 7: Heterogeneity plots by hMOA and timing of intervention**



Plot of I2 (heterogeneity measure) by mechanism of action of intervention, stratified by timing of intervention.