Table 3, Chapter 20. Delirium prevention—single interventions

| **Author/Year** | **Description of PSP** | **Study Design and patients** | **Theory or Logic Model** | **Description of Organization** | **Implementation Details** | **Outcomes: Benefits** | **Outcomes: Harms** | **Influence of Contexts on Outcomes** | **Overall Risk of Bias** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Inpatient hospital care** | | | | | | | | | |
| Al-Aama et al. 201074  Canada | Low dose melatonin for patients with hip fracture | Double-blind RCT  145 patients aged ≥65 years admitted to internal medicine service | The article cites a theory that delirium may be related to abnormal tryptophan metabolism, which can be regulated by melatonin supplementa­tion | Internal medicine service in a tertiary care center | Study medication was administered (in double-blind fashion) daily between 1,800 and 2,400 h depending upon patient availability and medication administration schedules for up to 14 days | **Incidence of delirium:**  Melatonin: 2/56 (3.6%)  Placebo: 10/52 (19.2%)  RR = 0.19 (95% CI: 0.04-0.81)  P<0.02 | 2/61 patients on melatonin had side effects of nightmares or hallucinations | Not applicable | Moderate |
| Larsen et al. 201075  USA | Atypical antipsychotic  Perioperative olanzapine (5 mg orally before and after surgery) or placebo to prevent postop delirium in elderly patients after joint replacement surgery | Double-blind RCT  400 patients aged ≥65 years under-going elective knee or hip replace-ment surgery | Olanzapine is an antipsychotic with some prior evidence of efficacy for delirium treatment and prevention. | Academic hospital | Perioperative olanzapine (5 mg orally) or placebo was administered before and after surgery by nurses not involved in ongoing care of the patients. | **Incidence of delirium:**  Olanzapine: 28 (14.3%)  Placebo: 82 (40.2%)  RR = 0.36 (95% CI: 0.24-0.52)  P<0.0001  The difference was also significant in separate subgroups (knee replacement, hip replacement) | Severity of delirium was greater in the olanzapine group (DRS‑R-98 score: 16.44 vs. 14.5, p = 0.02), and lasted longer (2.2 vs. 1.6 days, p = 0.02). Medical complications did not differ significantly between groups. | Not applicable | Moderate |
| Prakanrattana and Prapaitrakool 200776  Thailand | Atypical antipsychotic  Risperidone (1 mg) or placebo taken orally (sublingually) a single time following cardiac surgery | Double-blind RCT  126 patients aged >40 years under­going elective cardiac surgery | Risperidone is an antipsychotic with some previous evidence of efficacy for treatment of delirium | Academic hospital | Risperidone (1 mg orally) or placebo was given by nurses when patients began to wake in the ICU | **Post-op delirium:**  Risperidone: 7/63 (11.1%)  Placebo: 20/63 (31.7%)  RR = 0.35 (95% CI: 0.16-0.77)  P = 0.009 | None reported (post-op complications did not differ significantly between groups) | Not applicable | Low |
| Sieber et al. 201012  USA | Light propofol sedation during hip repair surgery | Double-blind RCT  114 patients aged ≥65 years under-going hip fracture repair | The authors hypothesized that minimizing sedation depth during spinal anesthesia for hip fracture repair in elderly patients could decrease the occurrence of postop delirium | Academic medical center | Implemented by anesthesiologists during surgery. | **Post-op delirium:**  Light sedation: 11/57 (19%)  Deep sedation: 23/57 (40%)  RR = 0.48 (95% CI: 0.26-0.89)  P = 0.02 | Complication rates were similar in both groups.  Light sedation: 26/57 (46%)  Deep sedation: 30/57 (53%  p = 0.57 | Not applicable | Moderate |
| Maldonado et al. 200917  USA | Different types of post‑op sedation after cardiac surgery | RCT  118 patients aged ≥18 years under-going elective cardiac valve surgery | The authors hypothesized that dex­medetomidine may be associated with a lower incidence of delirium due to its pharmacologic properties | Academic medical center | Implemented in the ICU following cardiac surgery. Patients were randomized to three different sedatives. | **Post-op delirium (Intention-to-treat):**  Dexmedetomidine: 4/40 (10%)  Propofol: 16/36 (44%)  Midazolam: 17/40 (44%)  p<0.001  Per protocol analysis also significantly different (p<0.001) | Not reported | Not applicable | High |
| Shehabi et al. 200977  Australia | Sedation  Dexmede­tomidine vs. morphine, effect on prevalence of delirium in patients at least 60 years old after cardiac surgery | Double-blind RCT  306 patients aged ≥60 years under-going cardiac surgery | Dexmede­tomidine is a selective and potent α2 adrenergic receptor agonist. In theory, it’s specificity may provide an advantage for delirium prevention compared to other post‑surgical sedatives or analgesics | Two tertiary referral academic hospitals | Study drug infusion began at 3 ml/h within 1 h of admission to the ICU; dexmedetomidine dose was 0.1‑0.7 µg/kg; morphine dose was 10-70 µg/kg; a propofol infusion and/or boluses were given if deemed necessary for rapid control of hypertensive episodes or unplanned awakening; open label morphine was allowed in the dexmed group to achieve equivalent analgesia, and propofol was allowed in the morphine arm to maintain equivalent sedation; drug infusion was continued until removal of chest drains when patient was ready for discharge from ICU, or for up to 48 h of mechanical ventilation. | **Incident Delirium:**  Dexmedetomidine: 13/152 (8.6%)  Morphine: 22/147 (15%)  Rate Ratio: 0.57 (95% CI: 0.26-1.1), P = 0.09  **Duration of delirium, median:**  Dexmedetomidine: 2 days  Morphine: 5 days (95% CI: 1.1-6.7) P = 0.03 | Bradycardia occurred more often in Dex group (16.5%) than in the Morphine group (6.1%)  P = 0.006  Systolic hypotension occurred more often in Morphine group (38.1%) compared to Dex group (23%)  P = 0.006 | Not applicable | Moderate |
| Hudetz et al. 200978  USA | Anesthetic (NMDA receptor antagonist)  Ketamine during anesthetic induction in older patients undergoing cardiac surgery with CPB. | RCT  58 patients aged ≥55 years under-going cardiac surgery with CPB. | Citing prior evidence that ketamine may have neuro­protective effects, the authors hypothesized that a single dose of ketamine during anesthetic induction would attenuate postop delirium in older patients undergoing cardiac surgery with CPB. | Veterans Affairs medical center | Ketamine (0.5 mg/kg) or placebo was administered intravenously during anesthetic induction for cardiac surgery. | **Post-op delirium:**  Ketamine: 1/29 (3.4%)  Placebo: 9/29 (31%)  RR = 0.11 (95% CI: 0.02-0.81)  P = 0.01 | Not reported | Not applicable | Moderate |
| Mouzopoulos et al. 200979  Greece | Local anesthetic  Fascia iliac block prophylaxis (via Bupivacaine) for hip fracture patients | RCT  207 patients aged ≥70 years admitted for hip fracture | The authors cite prior studies suggesting that hip fracture patients are at increased risk of delirium due to severe pain; therefore, a fascia iliac block might prevent delirium by preventing severe pain. | Hospital (type not reported) (980 beds) | Bupivacaine was injected on admission (in blinded fashion) and repeated daily every 24 h until delirium occurrence or hip surgery; 24 hr after surgery it was re-administered and repeated daily until delirium occurrence or discharge. | **Incident delirium:**  Prophylaxis: 10.8% (11/102)  Placebo: 23.8% (25/105)  OR = 0.45 (95% CI: 0.23-0.87) | No complications other than 3 local hematomas at injection site which resolved spontaneous­ly | Not applicable | Moderate |
| Gamberini et al. 200980  Switzerland | Acetylchol-inesterase inhibitor  Rivastigmine administered every 8 hrs from night before surgery until 6th postop day in a high-risk group of elderly patients undergoing elective cardiac surgery with CPB | Double-blind RCT  120 patients aged ≥65 years under-going elective cardiac surgery with CPB | Based on prior studies suggesting cholinesterase inhibitors can successfully treat delirium, the authors hypothesized that short-term administration of oral rivastigmine would reduce the incidence of postop delirium in a high-risk group of elderly patients undergoing elective cardiac surgery with CPB | Academic hospital | Rivastigmine administered every 8 hrs as a colorless odorless solution from night before surgery until 6th postop day | **Incident delirium as assessed by CAM:**  Rivastigmine: 18/56 (32%)  Placebo: 17/57 (30%)  RR = 1.12 (95% CI: 0.50-2.48)  P = 0.80 | No significant between-group difference for any adverse events. | Not applicable | Low |
| Liptzin et al. 200581  USA | Acetylchol-inesterase inhibitor  Donepezil (given at 5 mg/day) or placebo for 14 days preop and 14 days postop in patients undergoing total joint replacement (knee or hip) | Double-blind RCT  80 patients aged ≥50 years under-going knee or joint replace-ment | Donepezil is a cholinesterase inhibitor (disruption in cholinergic transmission is thought to be in causal pathway of delirium) | Academic medical center | Each patient was evaluated before surgery then given either Donepezil (given at 5 mg/day) or placebo for 14 days preop and 14 days postop | **Post-op delirium:**  Donepezil: 8/39 (20.5%)  Control: 7/41 (17.1%)  Rate Ratio = 1.2 (95% CI: 0.6-2.6)  P = 0.69 | Not reported | Not applicable | Moderate |
| McCaffrey et al. 200682  USA | Music therapy (musical selection with bedside CD turned on 1‑3 times/day + standard postop care from anesthesia awakening time until discharged) for patients undergoing hip or knee surgery | RCT (music therapy + usual care vs. usual care alone)  124 patients aged ≥65 years under-going elective hip or knee surgery | Prior studies have shown evidence that music can improve cognition and calm agitated patients | Large tertiary care center | Nurses blinded to room designation made room assignments. Various CDs were available in the music therapy rooms. Music was played when patients were awakening from anesthesia. CD was set to play for 1 hour 4 times daily. Also, nurses were asked to turn on the music each time they entered the room, and family members and patients were instructed how to use the CD player. Research assistants checked that CD players were working and that the music and timing of play suited patient preferences. | **Patients who experienced acute confusion:**  Music therapy: 2/62 (3.2%)  Usual care: 36/62 (58.1%)  RR = 0.06 (95% CI: 0.01-0.22)  P<0.0001 | None reported | Not applicable | High |
| McCaffrey and Locsin 200483  USA | Music therapy (musical selection with bedside CD turned on 1‑3 times/day + standard postop care from anesthesia awakening time until discharged) for patients undergoing elective hip and knee surgery | RCT (music therapy + usual care vs. usual care alone)  66 patients aged ≥65 years under-going elective hip or knee surgery | Prior studies have shown evidence that music can improve cognition and calm agitated patients | Large tertiary care center | Nurses blinded to room designation made room assignments. Various CDs were available in the music therapy rooms. Music was played when patients were awakening from anesthesia. CD was set to play for 1 hour 3 times daily. Also, nurses were asked to turn on the music each time they entered the room, and family members and patients were instructed how to use the CD player. Research assistants checked that CD players were working and that the music and timing of play suited patient preferences. | Significantly fewer patients in the music therapy group had episodes of confusion and delirium (F = 19.568, P = 0.001) | None reported | Not applicable | High |
| Kalisvaart et al. 200584  The Netherlands | Typical antipsychotic  Haloperidol or placebo (0.5 mg 3 times daily) was started on admission and continued until 3 days postop to prevent delirium after hip surgery | Double-blind RCT  430 patients aged ≥70 years under-going hip surgery | Haloperidol is a dopamine antagonist which can enhance acetylcholine release. Since delirium is highly associated with cholinergic deficiency, the authors hypothesized that haloperidol may have an indirect beneficial effect on delirium. | Teaching hospital | Haloperidol (0.5 mg 3 times daily) or placebo was started on admission and continued until 3 days after surgery. Experienced geriatric nurses and geriatricians provided proactive geriatric consultation (based on a structured multimodal protocol) to all patients. | **Post-op delirium:**  Haloperidol: 32/212 (15.1%)  Placebo: 36/218 (16.5%)  RR = 0.91 (95% CI 0.59-1.42)  P = 0.69  **Duration of delirium (days):**  Haloperidol: 5.4±4.9  Placebo: 11.8±7.5  P<0.001 | No drug-related side effects were reported | Not applicable | Moderate |
| Aizawa et al. 200285  Japan | Benzo-diazepines  Diazepam + flunitrazepam drip infusion and pethidine drip infusion for first 3 days (day of operation and first 2 postop days) in patients undergoing gastro­intestinal surgery | RCT (delirium-free protocol [DFP] vs. non-DFP)  40 patients aged >70 years under-going gastro-intestinal surgery | Sleep-wake cycle disorders have been reported to be associated with postop delirium, so medications that target sleep cycle disorders might prevent delirium | A city hospital, no other details provided | Diazepam (0.1 mg/kg intramuscular) + flunitrazepam (0.04 mg/kg drip infusion) and pethidine (1 mg/kg drip infusion) at specific times during first 3 days (day of operation and first 2 postop days) | **Incidence of post-op delirium:**  DFP: 1/20 (5%)  Non-DFP: 7/20 (35%)  P = 0.023 | DFP was reported to cause “morning lethargy” in 8/20 patients (40%). No other side effects were reported. | Not applicable | High |
| **Long-term care** | | | | | | | | | |
| Mentes and Culp 200386  USA | Hydration (individually calculated fluid intake goal) over an 8-week period in nursing home residents aged ≥65 years | Quasi-RCT (random­ization by coin toss of different partici-pating facilities)  49 partici­pants aged ≥65 years | Prior studies have shown that chronic under-hydration may lead to delirium and other adverse events | 2 Veteran’s Administration (VA), 2 community nursing homes | All RNs responsible for coordinating implementation at their site received intensive training on intervention/ usual care implementation. The project director made weekly visits to each site to ensure that the protocol was being implemented. RNs were responsible for most implementation details with assistance from NAs. NAs were responsible for providing fluids for participants. | **Episodes of acute confusion:**  Treatment: 0/25 (0%)  Control: 2/24 (8.2%)  P = not significant | None reported | Not clear, but the possibility was raised that control group staff might have altered their standard hydration practices due to awareness of research staff data collection. | High |
| Moretti et al. 200487  Italy | Rivastigmine (3-6 mg/day) for 2 years in patients with vascular dementia | RCT (Rivastig-mine vs. cardio-aspirin)  246 patients aged 68-85 years with vascular dementia | Delirium in patients with vascular dementia might be due to lack of acetylcholine in the brain. Rivastigmine is an anti-cholinesterase inhibitor | Academic hospital | Rivastigmine (3‑6 mg/day) or aspirin (100 mg/day) for 2 years in patients with vascular dementia | **Patients with episodes of delirium during follow-up:**  Rivastigmine: 46/115 (40%)  Cardioaspirin: 71/115 (62%)  RR = 0.65 (95% CI: 0.50-0.85)  P<0.001  **Mean duration of delirium:**  Rivastigmine: 4 ±1.71 days  Cardioaspirin: 7.86 ±2.73 days  P<0.01 | Not reported | Not applicable | High |

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