 doi:10.1111/anae.12539

Review Article

The efficacy of peri-operative interventions to decrease postoperative delirium in non-cardiac surgery: a systematic review and meta-analysis.

Z. Moyce,[1] R. N. Rodseth[2] and B. M. Biccard[3]

1 Registrar, 2 Honorary Lecturer, 3 Honorary Associate Professor, Peri-operative Research Group, Department of Anaesthesia, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

Summary

The purpose of this meta-analysis was to determine the efficacy of peri-operative interventions in decreasing the incidence of postoperative delirium. An electronic search of four databases was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to. We included randomised controlled trials of non-cardiac surgery with a peri-operative intervention and that reported postoperative delirium, and identified 29 trials. Meta-analysis revealed that peri-operative geriatric consultation (OR 0.46, 95% CI 0.32–0.67) and lighter anaesthesia (OR 2.66, 95% CI 1.27–5.56) were associated with a decreased incidence of postoperative delirium. For the other interventions, the point estimate suggested possible protection with prophylactic haloperidol (OR 0.62, 95% CI 0.36–1.05), bright light therapy (OR 0.20, 95% CI 0.03–1.19) and general as opposed to regional anaesthesia (OR 0.76, 95% CI 0.47–1.23). This meta-analysis has shown that peri-operative geriatric consultations with multicomponent interventions and lighter anaesthesia are potentially effective in decreasing the incidence of postoperative delirium.

Correspondence to: B. M. Biccard
Email: biccardb@ukzn.ac.za
Accepted: 13 November 2013

Introduction

As the global population ages, so the number of elderly patients with more co-morbidities requiring surgical interventions and procedures is increasing [1, 2]. These patients represent a significant proportion of the estimated annual 200 million surgical procedures conducted globally [3].

Postoperative delirium is associated with serious postoperative complications [2], which decrease functional capacity, prolong recovery and discharge, and directly increase healthcare costs [2, 4–8]. Patients suffering delirium have increased numbers of surgical complications, including fractures, urinary and respiratory tract infections, and vascular events [8]. Delirium also increases long-term morbidity through delayed functional and cognitive recovery [9], subsequent institutionalisation [5, 6] and postoperative depression [4].

Outcomes could be improved by systematic identification of important risk factors for delirium and identification of preventative measures that decrease the incidence of delirium and the subsequent associated morbidity [10]. The purpose of this systematic review and meta-analysis was to determine the efficacy of pharmacological and non-pharmacological peri-operative interventions to decrease delirium.

Methods

Using the PICOT (patient/intervention/comparison/outcome/time) question structure [11], we posed the following research question: 'Which peri-operative interventions during non-cardiac surgery have been independently associated with a reduction in delirium within the first seven postoperative days?' The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed [12]. Trials were considered eligible if they tested a peri-operative intervention aimed at reducing delirium after non-cardiac surgery in a randomised controlled manner. The primary outcome was the incidence of delirium within seven days of surgery. Eligible trials had to diagnose delirium using a test recommended by the Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-III; DSM-III-R; DSM IV [13]; or by the International Classification of Diseases, 10th edition [14]. We also included trials that used pre-operative and postoperative mini-mental state examinations in the diagnosis of delirium.

We searched four databases: Ovid Healthstar 1966 to Jan 2012; Ovid Medline 1946 to March 2012; EMBASE 1974 to August 2012; and the Cochrane Library to March 2012. The search terms included: (delirium).mp; (cognitive disorder).mp; and (surgery).mp. Exclusions were (cardiac surgery or coronary artery bypass or CABG).mp. The search was limited to English language, human and adult. All reviews, letters, case reports, comment, editorials and guidelines were removed, as were duplicate publications (Appendix 1). A manual search of the reference lists of all included papers was also conducted for further eligible studies. Concordance of article extraction was determined using a kappa statistic. Using a standardised data extraction sheet, we extracted data on: the outcome of delirium following a peri-operative intervention; the specific intervention tested; patient age; type of surgery; and the use of premedication. The quality of each study was assessed using the Jadad score (Appendix 2) [15].

Meta-analysis was conducted using Review Manager Version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2011). Heterogeneity between studies was assessed using univariate chi-squared analysis. Random or fixed effects models were used based on the presence or absence of significant heterogeneity between studies, respectively. Pooled dichotomous outcomes were reported as odds ratios (OR) with 95% CI. Where an intervention was associated with benefit, a funnel plot was constructed to determine if the outcomes reported were affected by publication bias. For interventions that were not significantly associated with a decrease in delirium, a power analysis was conducted to determine if the sample size was adequately powered for the outcome. The power analysis was based on the incidence in the control group, with an expected 25% relative risk reduction for an efficacious intervention.

Results

We identified 1376 studies from our literature search, of which 56 studies were selected for full paper analysis; the kappa statistic was 83%. From these studies, 29 were finally included in our meta-analysis (Fig. 1). Nineteen of the studies were of a high quality with a Jadad score of 4 or 5 [16–34], and 10 were low-quality studies with a Jadad score < 4 (Table 1) [35–44].

The following interventions to decrease delirium were tested in more than one trial and a meta-analysis was therefore possible (Figs. 2–9): geriatric (or multicomponent) consultation vs standard care, where peri-operative geriatric consultation constituted a proactive, comprehensive geriatric assessment along with management and rehabilitation to decrease the outcome of delirium [36, 38, 40]; deep vs light anaesthesia [19, 20, 32]; intravenous vs inhalational anaesthesia [18, 29]; general vs regional anaesthesia [30, 34, 43]; haloperidol vs placebo [21, 33, 37]; donepezil (a cholinesterase inhibitor) vs placebo [26, 27, 31]; gabapentin vs placebo [16, 25]; and bright light therapy vs standard care [41, 42]. Bright light therapy was instituted after extubation of the trachea and study patients received two hours of bright light therapy daily.

Only two interventions were associated with significantly decreased delirium: peri-operative geriatric consultation (Fig. 2) and light as opposed to deep

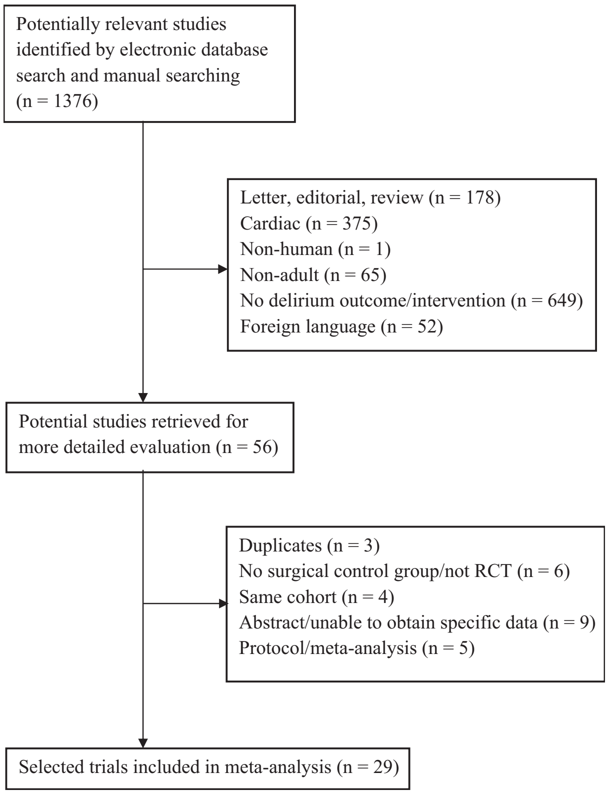

Figure 1 Flow chart of identification of randomised controlled trials included in the meta-analysis.

anaesthesia (Fig. 3). There was no significant heterogeneity for these two interventions. The funnel plot suggested that there was no publication bias associated with peri-operative geriatric consultations and delirium. However, there may have been publication bias with deep vs light anaesthesia (Fig. 10). The peri-operative geriatric consultation studies were of poorer quality (Jadad scores ≤ 3), largely due to inadequacies in randomisation and/or blinding. Depth of anaesthesia studies were good quality studies, (Jadad scores > 3). For the other interventions, the point estimate suggested possible protection with the use of prophylactic haloperidol, bright light therapy and general as opposed to regional anaesthesia. The power analyses showed that the sample size was inadequate for all the interventions included in the meta-analysis, with the exception of the peri-operative geriatric consultation.

Interventions that were reported in single trials included: pharmacological sleep–wake rhythm control vs control ($p = 0.023$) [35]; intrathecal morphine vs patient controlled morphine (no significant difference) [17]; continuation of antidepressant therapy vs control ($p = 0.05$) [22]; nitrous oxide vs oxygen ($p = 0.78$) [24]; patient-controlled epidural analgesia vs patient-controlled analgesia ($p < 0.05$) [39]; fascia iliac compartment block vs control (OR 0.45, 95% CI 0.23–0.87) [28]; and desflurane vs sevoflurane (no significant difference) [44].

Discussion

The main findings of this meta-analysis are that peri-operative geriatric consultations, which included multi-component interventions, and lighter as opposed to deeper anaesthesia were effective in decreasing postoperative delirium. The point estimate for peri-operative geriatric consultation was robust without heterogeneity, yet these clinical trials are at a high risk of bias due to inadequate randomisation and/or blinding. The point estimate for deep vs light anaesthesia showed significant heterogeneity, and there may be publication bias associated with this intervention.

Postoperative delirium occurs commonly among geriatric patients after both non-cardiac and cardiac surgery, with a reported incidence as high as 73% [2, 4]. It is characterised by acute cognitive decline after surgery associated with altered perception, attention and inappropriate behaviour [5, 6]. There are two standard definitions used for delirium: an acute and fluctuating disturbance of consciousness with signs of inattention, accompanied by a change in cognition and perception [13]; or an aetiologically non-specific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking and memory, including disturbances of emotion, psychomotor and the sleep–wake cycle [14]. Delirium is usually apparent on the first or second day postoperatively and symptoms usually worsen at night [7].

Delirium is a common complication following hip fracture surgery and the three trials of peri-operative geriatric consultations were conducted in this population. Multi-component and systemic assessment addressed urinary tract infections, hypoxia, anaemia, constipation, sleep disorders and nutritional deficiencies, which may all have a role in the aetiology and duration of delirium [38]. This meta-analysis lends support to multidisciplinary peri-operative medicine interventions to decrease delirium.

Table 1 Characteristics of included studies with peri-operative interventions to decrease postoperative delirium. Values are mean (SD) or number.

Study	Intervention	Assessment of POD	Timing of evaluation	Age; years	Type of surgery	Type of anaesthesia	Premedication	Jadad score [15]
Aizawa et al. [35], 2002	Control of sleep–wake rhythm vs control	DSM IV	Day 1–6	I: 76 (5) C: 76 (4)	Abdominal	GA + epidural	NR	3
Akarsu et al. [16], 2012	Pregabalin vs control	MMSE	Day 1–10	44–68	Abdominal	GA: TIVA	Nil	4
Beaussier et al. [17], 2006	Intrathecal morphine vs IV PCA morphine	CAM	Day 1	78 (5)	Abdominal	GA	Hydroxyzine 1 mg.kg^{-1}	5
Cai et al. [18], 2012	IV vs inhalational	MMSE ≤ 25	Day 1, 3, 5, 8, 15	70.1 (4.6)	Non-cardiovascular	GA	Diazepam 10 mg, atropine 0.5 mg	4
Chan et al. [19], 2013	BIS guided vs routine care	DSM III	Day 1	I:68.1 (8.2) C:67.6 (8.3)	Non-cardiovascular	GA	NR	5
Deschodt et al. [36], 2012	IGCT vs standard care	CAM	Day 1–3	I: 80.4 (7) C:81.1 (7.2)	Orthopaedic	NR	NR	1
Jildenstal et al. [20], 2011	AEP vs control	MMSE < 25	Day 1–3	I:18–92 C:19–91	Ophthalmic	GA	Midazolam, paracetamol 1 g	4
Kalisvaart et al. [21], 2005	Haloperidol vs placebo	DSM IV, CAM, DRS	Day 1–3	I:78.7 (0.64) C:79.5 (6.27)	Orthopaedic	NR	NR	5
Kaneko et al. [37], 1999	Haloperidol vs placebo	DSM IIIR	Day 1–8	I:72.4 (8.2) C:73.1 (9.3)	Abdominal	NR	NR	3
Kudoh et al. [22], 2002	Antidepressant continued vs stopped	CAM	Day 1–2	I: 49.5 (9.4) C:50.5 (7.9)	Non-cardiovascular	GA	NR	4
Larsen et al. [23], 2010	Olanzapine vs placebo	DSM IIIR, CAM	Day 1–3	I:73.4 (6.1) C:74 (6.2)	Orthopaedic	GA or regional	Midazolam 1–2 mg, fentanyl	5
Leung et al. [24], 2006	N_2O vs O_2	DSM IIIR, CAM	NR	I: (65–95) C: (65–88)	Non-cardiovascular	GA	Fentanyl 2 μg.kg^{-1}	4
Leung et al. [25] 2006	Gabapentin vs placebo	DSM IIIR, CAM	Day 1–3	I:57.2 (10.3) C:61.4 (11.3)	Spinal	GA	NR	4

Table 1. (continued)

Study	Intervention	Assessment of POD	Timing of evaluation	Age; years	Type of surgery	Type of anaesthesia	Premedication	Jadad score [15]
Liptzin et al. [26], 2005	Donepezil vs placebo	DSM IV, CAM	Day 1–5	67.2 (8.7)	Orthopaedic	NR	NR	5
Lundstrom et al. [38], 2007	Intervention geriatric programme vs conventional care	DSM IV	Day 1	I: 82.3 (6.6) C: 82 (5.6)	Orthopaedic	Regional/GA	NR	3
Mann et al. [39], 2000	PCA vs PCEA	DSM III	Day 1–7	I: 76.8 (4.7) C:76.1 (5.6)	Abdominal	GA	Hydroxyzine 100 mg	3
Marcantonio et al. [40], 2001	Geriatric consultation vs usual	CAM	Day 1	I: 78 (8) C: 80 (8)	Orthopaedic	NR	NR	3
Marcantonio et al. [27], 2011	Donepezil vs placebo	CAM	Day 1–3	I: 88 (5.2) C: 87 (3.7)	Orthopaedic	NR	NR	5
Mouzopoulos et al. [28], 2009	Fascia iliaca compartment block vs placebo	DSM IV, CAM	Day 1–6	I: 72 (4) C:73 (4)	Orthopaedic	Epidural	NR	4
Nishikawa et al. [29], 2004	Propofol vs sevoflurane	DRS, DSM III	Day 1–3	I: 71 (8) C: 71 (7)	Abdominal	GA/epidural	nil	4
Ono et al. [41], 2011	Bright light vs control	NEECHAM, DSM IV-TR	Day 1–3	I:63.4 (9.7) C:63.8 (7.8)	Thoracic	GA	NR	3
Papaioanno et al. [30], 2005	GA vs regional	DSM III	Day 2,3	> 60	Orthopaedic, urology, vascular		NR	4
Sampson et al. [31], 2007	Donepezil vs placebo	DSM IV	Day 1–5	52–86 (67.8)	Orthopaedic	NR	NR	5
Sieber et al. [32], 2010	Deep vs light sedation	CAM	Day 1–3	I: 81.8 (6.7) C: 81.2 (7.6)	Orthopaedic	Spinal	NR	5
Slor et al. [34],	GA vs regional	DSM IV, CAM	Day 1–7	I:76.7 (5.5) C:78.2 (6.8)	Non-cardiovascular	GA and regional	NR	5
Taguchi et al. [42], 2007	Bright light vs control	NEECHAM	Day 1–7	29–71	Thoracic	GA	NR	3

Table 1. (continued)

Study	Intervention	Assessment of POD	Timing of evaluation	Age; years	Type of surgery	Type of anaesthesia	Premedication	Jadad score [15]
Wang et al. [33] 2012	Haloperidol vs placebo	CAM	Day 1	I:74 (5.8) C: 74.4 (7.0)	Non-cardiovascular	GA/regional/ GA + regional	NR	5
Berggren et al. [43] 1987	GA vs regional	DSM III	Day 1–7	I:77 (7) C:78 (8)	Orthopaedics	GA and regional	Pethidine 25–50 mg	3
Chen et al. [44], 2001	Desflurane vs sevoflurane	MMSE	Day 1	I: 75 (8) C: 73 (9)	Orthopaedics	GA	Midazolam 1 mg	3

POD, postoperative delirium; DSM, Diagnostic and Statistical Manual of Mental Disorders; I, intervention; C, control; GA, general anaesthesia; NR, not reported; MMSE, Mini-mental state exam; TIVA, total intravenous anaesthesia; CAM, confusion assessment method; IV, intravenous; PCA, patient-controlled analgesia; BIS, bispectral index; IGCT, inpatient geriatric consultation team; AEP, auditory evoked potential; DRS, delirium rating scale; PCEA, patient-controlled epidural analgesia; NEECHAM, Neelon and Champagne confusion scale.

Delirium is multifactorial, and anaesthetic technique is another potentially modifiable risk factor [12, 13]. Intra-operative monitoring of depth of anaesthesia using bispectral index (BIS) or auditory evoked potentials has shown to facilitate titration of anaesthetic drugs. Bispectral index values between 40 and 60 during anaesthesia have been associated with decreased awareness, earlier recovery profiles and faster emergence [19]. Chan et al. demonstrated that titrating anaesthetic agents to maintain BIS between 40 and 60 and avoiding episodes of deep anaesthesia (BIS < 40) reduced the risk of delirium ($p = 0.01$) [19]. Sieber et al. found that light sedation (BIS > 80) during spinal anaesthesia for orthopaedic surgery decreased the occurrence of delirium by 50% when compared with deep sedation (BIS ~50) ($p = 0.02$) [32]. Depth of anaesthesia guided by auditory evoked potentials demonstrated that patients with lighter anaesthesia sustained fewer intra-operative events, had higher blood pressure, required less fluids or vasopressors, and were at a lower risk of developing early postoperative decline [20].

Regarding the intra-operative measures that were identified, neither intravenous vs inhalational anaesthesia, nor regional vs general anaesthesia, showed any effect on postoperative delirium. Although both of these analyses were underpowered, the point estimates favoured inhalational and general anaesthesia. In contrast, another meta-analysis of the efficacy of general and regional anaesthesia failed to show a significant difference (five studies), and suggested that general anaesthesia may increase the risk of developing postoperative cognitive dysfunction [45].

Our meta-analysis has found a trend to protection with the use of haloperidol. The dose of haloperidol varied between the studies. Wang et al. used 0.5 mg haloperidol as an intravenous bolus postoperatively, followed by an infusion at 0.1 $mg.h^{-1}$ for 12 h; Kaneko et al. administered 5 mg haloperidol intravenously per day for five days, and Kalisvaart et al. used oral haloperidol 1.5 mg pre-operatively and for three days postoperatively [21, 33, 37]. A recent meta-analysis conducted by Teslyar et al. looked at antipsychotics as a group (haloperidol, olanzapine and risperidone) and they also showed a trend to a reduction in delirium with the peri-operative use of antipsychotics [46].

Study or subgroup	Geriatric consultation Events	Total	Usual care Events	Total	Weight%	Odds ratio M-H, Fixed, 95% CI
Deschodt 2012	35	94	41	77	33.9	0.52 (0.28, 0.96)
Lundstrom 2007	56	102	73	97	40.5	0.40 (0.22, 0.73)
Marcantonio 2001	20	62	32	64	25.6	0.48 (0.23, 0.98)
Total (95% CI)		**258**		**238**	**100.0**	**0.46 (0.32, 0.67)**
Total events	111		146			

Heterogeneity: Chi² = 0.37, d.f. = 2 (p = 0.83); I² = 0%
Test for overall effect: Z = 4.11 (p < 0.0001)

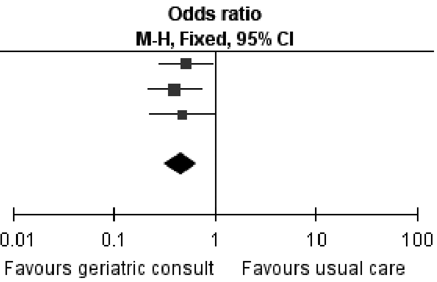

Figure 2 Meta-analysis of the efficacy of peri-operative geriatric consultation vs standard care on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	Deep anaesthesia Events	Total	Light anaesthesia Events	Total	Weight%	Odds ratio M-H, Random, 95% CI
Chan 2013	109	452	70	450	50.4	1.73 (1.24, 2.41)
Jildenstal 2011	16	226	2	224	17.2	8.46 (1.92, 37.23)
Sieber 2010	23	57	11	57	32.4	2.83 (1.22, 6.58)
Total (95% CI)		**735**		**731**	**100.0**	**2.66 (1.27, 5.56)**
Total events	148		83			

Heterogeneity: Tau² = 0.25; Chi² = 5.09, d.f. = 2 (p = 0.08); I² = 61%
Test for overall effect: Z = 2.60 (p = 0.009)

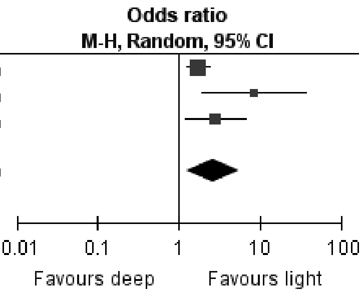

Figure 3 Meta-analysis of the efficacy of depth of anaesthesia vs standard care on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	Intravenous Events	Total	Inhalational Events	Total	Weight%	Odds ratio M-H, Random, 95% CI
Cai 2012	46	1000	220	1000	0.0	0.17 (0.12, 0.24)
Hocker 2009	25	51	22	50	72.1	1.22 (0.56, 2.68)
Nishikawa 2004	4	25	0	25	27.9	10.67 (0.54, 209.64)
Total (95% CI)		**76**		**75**	**100.0**	**2.24 (0.32, 15.54)**
Total events	29		22			

Heterogeneity: Tau² = 1.20; Chi² = 1.97, d.f. = 1 (p = 0.16); I² = 49%
Test for overall effect: Z = 0.82 (p = 0.41)

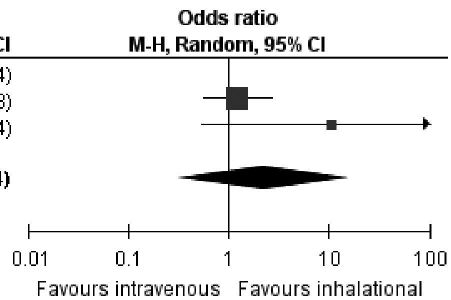

Figure 4 Meta-analysis of the efficacy of intravenous vs inhalational anaesthesia on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	General anaesthesia Events	Total	Regional anaesthesia Events	Total	Weight%	Odds ratio M-H, Fixed, 95% CI
Berggen 1987	11	29	14	28	22.7	0.61 (0.21, 1.75)
Papaioannou 2005	6	28	3	19	7.2	1.45 (0.32, 6.71)
Slor 2011	18	189	42	337	70.1	0.74 (0.41, 1.33)
Total (95% CI)		**246**		**384**	**100.0**	**0.76 (0.47, 1.23)**
Total events	35		59			

Heterogeneity: Chi² = 0.87, d.f. = 2 (p = 0.65); I² = 0%
Test for overall effect: Z = 1.11 (p = 0.27)

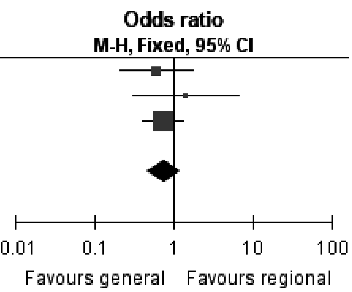

Figure 5 Meta-analysis of the efficacy of general vs regional anaesthesia on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	Haloperidol Events	Haloperidol Total	Placebo Events	Placebo Total	Weight%	Odds ratio M-H, Random, 95% CI
Kalisvaart 2005	32	212	36	218	41.2	0.90 (0.53, 1.51)
Kaneko 1999	4	38	13	40	14.6	0.24 (0.07, 0.84)
Wang 2012	35	229	53	228	44.2	0.60 (0.37, 0.96)
Total (95% CI)		**479**		**486**	**100.0**	**0.62 (0.36, 1.05)**
Total events	71		102			

Heterogeneity: Tau² = 0.11; Chi² = 4.05, d.f. = 2 (p = 0.13); I² = 51%
Test for overall effect: Z = 1.77 (p = 0.08)

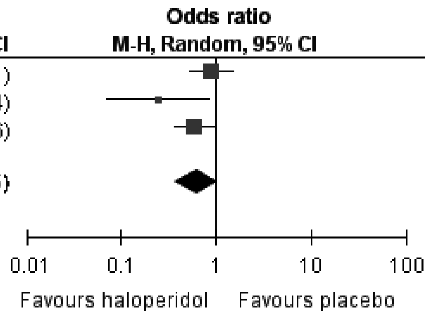

Figure 6 Meta-analysis of the efficacy of haloperidol on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	Donepezil Events	Donepezil Total	Placebo Events	Placebo Total	Weight%	Odds ratio M-H, Random, 95% CI
Liptzin 2005	8	39	7	41	47.9	1.25 (0.41, 3.86)
Marcantonio 2011	7	11	9	14	28.2	0.97 (0.19, 5.03)
Sampson 2007	2	19	5	14	23.9	0.21 (0.03, 1.32)
Total (95% CI)		**69**		**69**	**100.0**	**0.76 (0.28, 2.06)**
Total events	17		21			

Heterogeneity: Tau² = 0.21; Chi² = 2.70, d.f. = 2 (p = 0.26); I² = 26%
Test for overall effect: Z = 0.53 (p = 0.59)

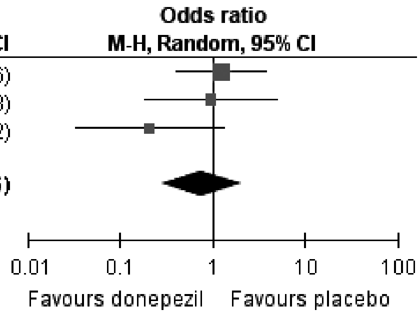

Figure 7 Meta-analysis of the efficacy of donepezil on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	Gabapentin Events	Gabapentin Total	Placebo Events	Placebo Total	Weight%	Odds ratio M-H, Random, 95% CI
Akarsu 2012	0	30	0	30		Not estimable
Leung 2006	0	9	5	12	100.0	0.07 (0.00, 1.51)
Total (95% CI)		**9**		**12**	**100.0**	**0.07 (0.00, 1.51)**
Total events	0		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.69 (p = 0.09)

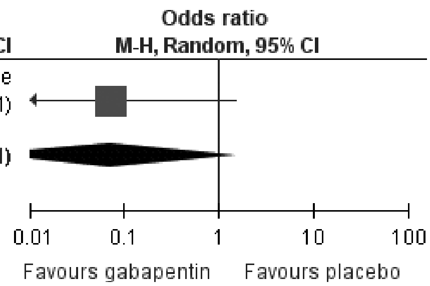

Figure 8 Meta-analysis of the efficacy of peri-operative gabapentin on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Study or subgroup	Bright light therapy Events	Bright light therapy Total	Control Events	Control Total	Weight%	Odds ratio M-H, Fixed, 95% CI
Ono 2011	1	10	5	12	69.2	0.16 (0.01, 1.65)
Taguchi 2007	1	6	2	5	30.8	0.30 (0.02, 4.91)
Total (95% CI)		**16**		**17**	**100.0**	**0.20 (0.03, 1.19)**
Total events	2		7			

Heterogeneity: Chi² = 0.12, d.f. = 1 (p = 0.72); I² = 0%
Test for overall effect: Z = 1.77 (p = 0.08)

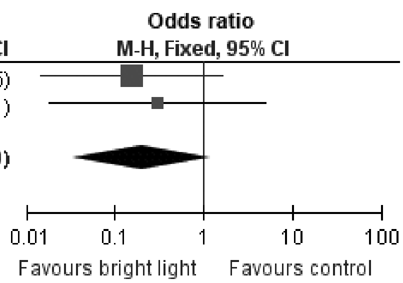

Figure 9 Meta-analysis of the efficacy of bright light therapy on outcome of postoperative delirium. M-H, Mantel-Haenszel.

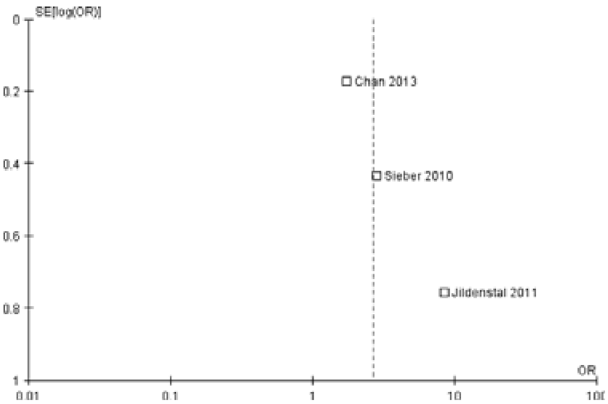

Figure 10 Funnel plot for light vs deep anaesthesia.

Gabapentin and pregablin are γ-aminobutyric acid analogues that were developed as anticonvulsants, and recent evidence supports their use for chronic pain. In the postoperative period, they reduce pain and decrease opioid consumption. A pilot study by Leung et al. found that postoperative use of gabapentin decreased the incidence of delirium, and concluded that this was probably secondary to an opioid sparing effect [16, 25].

There is a close relationship between sleep disorders and the development of delirium [35]. Our meta-analysis found a trend to improved outcome in patients maintaining a sleep–wake cycle using bright light therapy. However, this intervention was also underpowered.

Due to the multifactorial nature of delirium, we are most likely to realise benefit when multiple interventions are instituted. This meta-analysis supports this approach where peri-operative geriatric consultations have been shown to be a potentially very powerful intervention to decrease delirium. We recommend that future interventional trials for delirium should consider a multi-component approach to preventing delirium.

There are a number of limitations to this meta-analysis. Firstly, of all the possible interventions investigated to decrease delirium, only peri-operative geriatric consultation and light vs deep anaesthesia were adequately powered. It is therefore possible that certain of the other interventions are efficacious; however, further research would be required to confirm this. Secondly, peri-operative geriatric consultation studies were limited to orthopaedic surgery. This research needs to be extended to other non-cardiac surgeries. Furthermore, the nature of multi-component consultations makes it difficult to exclude a strong bias due to poor randomisation and blinding, which is evident in this meta-analysis. In the pharmacological intervention studies, there was no standardisation of the anaesthetic technique. This is an important limitation, as this meta-analysis suggested that depth of anaesthesia may be an important determinant of delirium. Furthermore, there was no standardisation of the dosage of the pharmacological intervention between the trials analysed and this may be an important confounder in some studies. We also excluded foreign language studies, which could have impacted on the results of the meta-analysis. Finally, few studies assessed pre-operative risk for delirium, with no standardisation in timing of postoperative testing either. A standardised protocol for pre-operative risk assessment and outcome determination would be desirable in future studies.

In conclusion, the main findings of this meta-analysis are that peri-operative geriatric consultations that involve multi-component interventions, and lighter anaesthesia, are potentially effective in decreasing the outcome of delirium.

Competing interests

No external funding and no competing interests declared.

References

1. Robinson TN, Raeburn CD, Tran ZV, Brenner LA, Moss M. Motor subtypes of postoperative delirium in older adults. *Archives of Surgery* 2011; **146**: 295–300.
2. Bekker AY, Weeks EJ. Cognitive function after anaesthesia in the elderly. *Best Practice and Research in Clinical Anaesthesiology* 2003; **17**: 259–72.
3. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**: 139–44.
4. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia* 2008; **63**: 941–7.
5. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *British Journal of Anaesthesia* 2009; **103**(Suppl 1): i41–6.
6. Bilotta F, Doronzio A, Stazi E, et al. Early postoperative cognitive dysfunction and postoperative delirium after anaesthesia with various hypnotics: study protocol for a randomised controlled trial–the PINOCCHIO trial. *Trials* 2011; **12**: 170.

7. Steinmetz J, Rasmussen LS. The elderly and general anesthesia. *Minerva Anestesiologica* 2010; **76**: 745–52.
8. Laurila JV, Laakkonen ML, Tilvis RS, Pitkala KH. Predisposing and precipitating factors for delirium in a frail geriatric population. *Journal of Psychosomatic Research* 2008; **65**: 249–54.
9. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesthesia and Analgesia* 2011; **112**: 1202–11.
10. Patti R, Saitta M, Cusumano G, Termine G, Di Vita G. Risk factors for postoperative delirium after colorectal surgery for carcinoma. *European Journal of Oncology Nursing* 2011; **15**: 519–23.
11. Thabane L, Thomas T, Ye C, Paul J. Posing the research question: not so simple. *Canadian Journal of Anesthesia* 2009; **56**: 71–9.
12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 2009; **339**: b2535.
13. American Psychiatric Association. *Diagnostic and statistic manual of mental disorders*, 4th edn. (text revision) (DSM-IV-TR). Washington, DC, 2000. doi:10.1176/appi.books.9780890423349 (accessed 28/10/2013).
14. World Health Organization. International Classification of Diseases (ICD). http://www.who.int/classifications/icd/en/ (accessed 28/10/2013).
15. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; **17**: 1–12.
16. Akarsu T, Tur H, Bolat C, Ozkaynak I. Comparison of pre-emptive pregabalin with placebo and diclofenac combination for postoperative analgesia and cognitive functions after laparoscopic cholecystectomy. *Turkiye Klinikleri Journal of Medical Sciences* 2012; **32**: 963–70.
17. Beaussier M, Weickmans H, Parc Y, et al. Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. *Regional Anesthesia and Pain Medicine* 2006; **31**: 531–8.
18. Cai Y, Hu H, Liu P, et al. Association between the apolipoprotein E4 and postoperative cognitive dysfunction in elderly patients undergoing intravenous anesthesia and inhalation anesthesia. *Anesthesiology* 2012; **116**: 84–93.
19. Chan MT, Cheng BC, Lee TM, Gin T, CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *Journal of Neurosurgical Anesthesiology* 2013; **25**: 33–42.
20. Jildenstål PK, Hallén JL, Rawal N, Gupta A, Berggren L. Effect of auditory evoked potential-guided anaesthesia on consumption of anaesthetics and early postoperative cognitive dysfunction: a randomised controlled trial. *European Journal of Anaesthesiology* 2011; **28**: 213–9.
21. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *Journal of the American Geriatrics Society* 2005; **53**: 1658–66.
22. Kudoh A, Katagai H, Takazawa T. Antidepressant treatment for chronic depressed patients should not be discontinued prior to anesthesia. *Canadian Journal of Anesthesia* 2002; **49**: 132–6.
23. Larsen KA, Kelly SE, Stern TA, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics* 2010; **51**: 409–18.
24. Leung JM, Sands LP, Vaurio LE, Wang Y. Nitrous oxide does not change the incidence of postoperative delirium or cognitive decline in elderly surgical patients. *British Journal of Anaesthesia* 2006; **96**: 754–60.
25. Leung JM, Sands LP, Rico M, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. *Neurology* 2006; **67**: 1251–3.
26. Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *American Journal of Geriatric Psychiatry* 2005; **13**: 1100–6.
27. Marcantonio ER, Palihnich K, Appleton P, Davis RB. Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. *Journal of the American Geriatrics Society* 2011; **59** (Suppl 2): S282–8.
28. Mouzopoulos G, Vasiliadis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. *Journal of Orthopaedics and Traumatology* 2009; **10**: 127–33.
29. Nishikawa K, Nakayama M, Omote K, Namiki A. Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients: propofol-based vs. sevoflurane-based anesthesia. *Acta Anaesthesiologica Scandinavica* 2004; **48**: 162–8.
30. Papaioannou A, Fraidakis O, Michaloudis D, Balalis C, Askitopoulou H. The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients. *European Journal of Anaesthesiology* 2005; **22**: 492–9.
31. Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *International Journal of Geriatric Psychiatry* 2007; **22**: 343–9.
32. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clinic Proceedings* 2010; **85**: 18–26.
33. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. *Critical Care Medicine* 2012; **40**: 731–9.
34. Slor CJ, de Jonghe JF, Vreeswijk R, et al. Anesthesia and postoperative delirium in older adults undergoing hip surgery. *Journal of the American Geriatrics Society* 2011; **59**: 1313–9.
35. Aizawa K, Kanai T, Saikawa Y, et al. A novel approach to the prevention of postoperative delirium in the elderly after gastrointestinal surgery. *Surgery Today* 2002; **32**: 310–4.
36. Deschodt M, Braes T, Flamaing J, et al. Preventing delirium in older adults with recent hip fracture through multidisciplinary geriatric consultation. *Journal of the American Geriatrics Society* 2012; **60**: 733–9.
37. Kaneko T, Cai J, Ishikura T, Kobayashi M, Naka T, Kaibara N. Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery. *Yonago Acta Medica* 1999; **42**: 179–84.
38. Lundström M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. *Aging Clinical and Experimental Research* 2007; **19**: 178–86.
39. Mann C, Pouzeratte Y, Boccara G, et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000; **92**: 433–41.

40. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *Journal of the American Geriatrics Society* 2001; **49**: 516–22.
41. Ono H, Taguchi T, Kido Y, Fujino Y, Doki Y. The usefulness of bright light therapy for patients after oesophagectomy. *Intensive and Critical Care Nursing* 2011; **27**: 158–66.
42. Taguchi T, Yano M, Kido Y. Influence of bright light therapy on postoperative patients: a pilot study. *Intensive and Critical Care Nursing* 2007; **23**: 289–97.
43. Berggren D, Gustafson Y, Eriksson B, et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesthesia and Analgesia* 1987; **66**: 497–504.
44. Chen X, Zhao M, White PF, et al. The recovery of cognitive function after general anesthesia in elderly patients: a comparison of desflurane and sevoflurane. *Anesthesia and Analgesia* 2001; **93**: 1489–94.
45. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. *Journal of Alzheimer's Disease* 2010; **22**(Suppl 3): 67–79.
46. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. *Psychosomatics* 2013; **54**: 124–31.

Appendix 1

Search strategy

Search	Terms
1	delirium.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
2	cognitive disorder.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
3	1 or 2
4	surgery.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
5	3 and 4
6	remove duplicates from 5
7	limit 6 to humans
8	limit 7 to "all adult (19 plus years)"
9	8 not "review".mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
10	9 not "All Child".mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]
11	9 not "pediatric".mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]

Appendix 2

Jadad score used to measure the likelihood of bias of studies included in the meta-analysis [15]

Category	Criteria	Score: Yes = 1 No = 0
Randomisation	Is study described as randomised?	
	Is randomisation appropriate?	
Blinding	Is the study described as double blind?	
	Is blinding appropriate/single blind?	
Withdrawals/dropouts	Is there a description of withdrawal or dropouts?	

