Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial

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Summary

Background Delirium is frequently diagnosed in critically ill patients and is associated with poor clinical outcomes. Haloperidol is the most commonly used drug for delirium despite little evidence of its effectiveness. The aim of this study was to establish whether early treatment with haloperidol would decrease the time that survivors of critical illness spent in delirium or coma.

Methods We did this double-blind, placebo-controlled randomised trial in a general adult intensive care unit (ICU). Critically ill patients (≥18 years) needing mechanical ventilation within 72 h of admission were enrolled. Patients were randomised (by an independent nurse, in 1:1 ratio, with permuted block size of four and six, using a centralised, secure web-based randomisation service) to receive haloperidol 2·5 mg or 0·9% saline placebo intravenously every 8 h, irrespective of coma or delirium status. Study drug was discontinued on ICU discharge, once delirium-free and coma-free for 2 consecutive days, or after a maximum of 14 days of treatment, whichever came first. Delirium was assessed using the confusion assessment method for the ICU (CAM-ICU). The primary outcome was delirium-free and coma-free days, defined as the number of days in the first 14 days after randomisation during which the patient was alive without delirium and not in coma from any cause. Patients who died within the 14 day study period were recorded as having 0 days free of delirium and coma. ICU clinical and research staff and patients were masked to treatment throughout the study. Analyses were by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Registry, number ISRCTN83567338.

Findings 142 patients were randomised, 141 were included in the final analysis (71 haloperidol, 70 placebo). Patients in the haloperidol group spent about the same number of days alive, without delirium, and without coma as did patients in the placebo group (median 5 days [IQR 0–10] *vs* 6 days [0–11] days; p=0·53). The most common adverse events were oversedation (11 patients in the haloperidol group *vs* six in the placebo group) and QTc prolongation (seven patients in the haloperidol group *vs* six in the placebo group). No patient had a serious adverse event related to the study drug.

Interpretation These results do not support the hypothesis that haloperidol modifies duration of delirium in critically ill patients. Although haloperidol can be used safely in this population of patients, pending the results of trials in progress, the use of intravenous haloperidol should be reserved for short-term management of acute agitation.

Funding National Institute for Health Research.

Introduction

Delirium is a disorder characterised by acute brain dysfunction. Although causality between delirium and mortality is not established, critically ill patients who develop delirium are up to three times more likely to die by 6 months than are those who do not,[1] with each additional day of delirium being associated with a 10% increase in the risk of death.[2] Importantly, in mechanically ventilated patients delirium might be associated with long-term cognitive impairment.[3] The incidence of delirium in patients in critical care is reported to be about 30% overall,[4] but is 60–80% in sedated ventilated patients, excluding those admitted after major elective surgery.[1,5,6] A point prevalence study of 497 patients in intensive care units (ICUs) in 11 countries showed that 68% of patients were either over sedated or shown to have delirium.[7] 17 of 27 (63%) mechanically ventilated patients were shown to have delirium in a UK study.[8]

Delirium probably results from diverse pathophysiological mechanisms, including derangements of several neurotransmitter systems within the brain, but the underlying mechanisms are not fully understood. The most widely postulated theory is that delirium is caused by cholinergic deficiency with an excess of dopamine.[9] The main mechanisms of action of haloperidol are thought to be antagonism at cortical dopamine (D2) receptors, nigrostriatal pathway D2 blockade, and disinhibition of acetylcholine with acetylcholine increase.[9] Haloperidol is extensively protein-bound and rapidly distributed throughout the body with a mean elimination half life of 21 h. The rationale for use of haloperidol also includes a reduction in the need for psychotropic sedative and analgesic drugs in ventilated patients, which have been shown to contribute to the risk of delirium,[10] and potentially beneficial immunomodulatory effects.[11,12]

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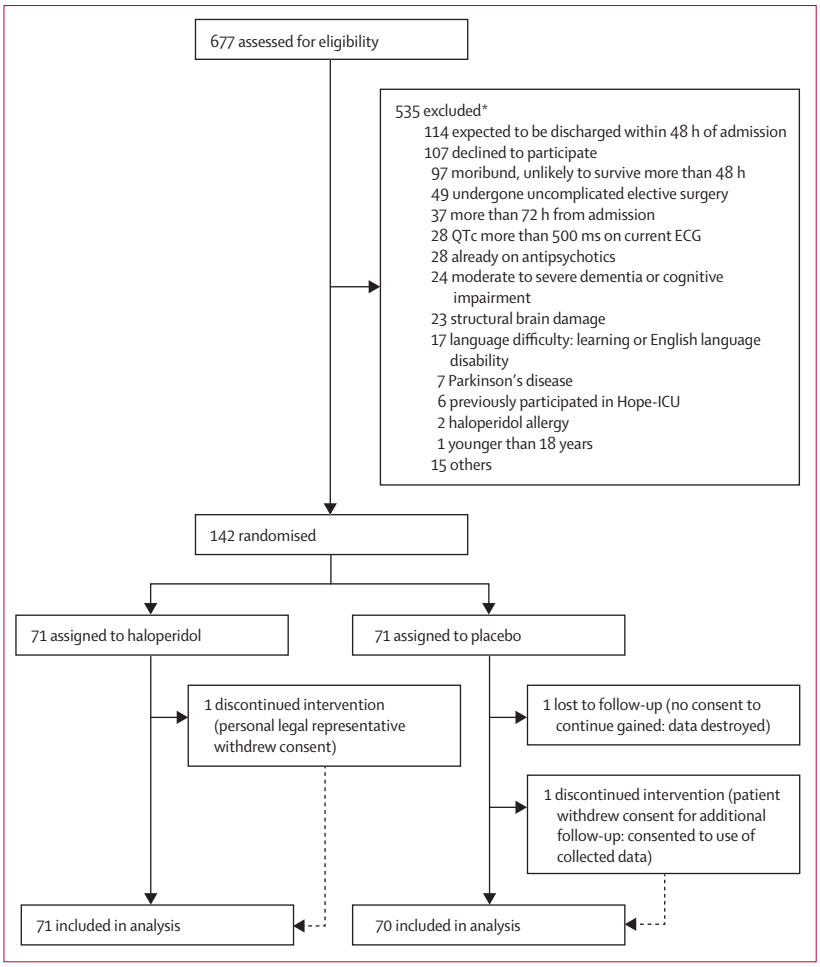

Figure 1: **Trial profile**
*20 patients had more than one reason for exclusion.

There is no reported evidence that treatment with haloperidol reduces incidence and duration of delirium in adult ICU patients.[13] Despite this absence of evidence, haloperidol is commonly used in clinical practice to prevent and treat delirium in critically ill patients and has been used as part of routine sedation practice and as a quality improvement intervention.[14,15] However, haloperidol is not innocuous because reports of harm associated with antipsychotic use in elderly patients are common.[16,17]

The aim of this trial was to test the hypothesis that in critically ill patients needing mechanical ventilation, early administration of intravenous haloperidol for the duration of the ICU stay or until delirium-free and coma-free for 48 h would reduce the frequency and duration of delirium and improve other important clinical outcomes.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled trial of intravenous haloperidol in adult (≥18 years) mechanically ventilated patients. Patients were recruited from the general mixed medical–surgical adult ICU in Watford General Hospital (Watford, UK). Patients were eligible for inclusion from the time they needed mechanical ventilation on the ICU, provided that was within 72 h of admission. Patients were excluded from the trial if they fulfilled any of the following criteria: allergy to haloperidol as established by direct questioning of family members and available medical history, moderate to severe dementia as documented by medical history, Parkinson's disease, structural brain damage, chronic antipsychotic use, corrected QTc interval (QTc) greater than 500 ms, history of torsades de pointes, history of neuroleptic malignant syndrome, family history of dystonic reactions to drugs, age younger than 18 years, pregnancy, moribund and not expected to survive 48 h, or predicted ICU stay of less than 48 h. Patients who had undergone elective uncomplicated surgery, or who had been involved in a clinical trial of an investigational medicinal product in the previous 30 days were also excluded. Patients who had been enrolled into the study once were not enrolled again if they were readmitted to the ICU.

Sedated, mechanically ventilated patients did not have capacity to give consent; therefore, consistent with requirements of the European Union clinical trial directive, a member of the research team (VJP, TA, or XBZ) obtained written informed consent from a personal or professional legal representative before randomisation. All surviving patients were informed about the trial at the earliest opportunity after regaining competence and then provided written consent to continue in the trial. The protocol was approved by the Berkshire Research Ethics Committee, the UK Medicines and Healthcare Products Regulatory Agency, and the Hertfordshire Hospitals Research and Development Consortium. The trial was coordinated by West Hertfordshire Hospitals National Health Service Trust in partnership with Warwick Clinical Trials Unit. An independent data monitoring and ethics committee monitored the trial for safety.

Randomisation and masking

A nurse from the operating theatre post-anaesthetic care unit (PACU), who was independent of the ICU clinical and research staff, allocated patients in a 1 to 1 ratio, with random permuted blocks of size four and six, to haloperidol or placebo, using a centralised, secure web-based randomisation service. Study drugs were prepared in the PACU, which is separate from the ICU, in identical 2 mm syringes by an independent member of the PACU nursing staff who then directly administered the drug to study patients. All ICU clinical and research staff, legal representatives, and the patients were masked to study drug. The data monitoring and safety committee reviewed blinded data reports. Statisticians were not masked to allocation. The success of masking was not formally assessed.

Procedures

Treatment was initiated within 72 h of admission to ICU, irrespective of coma or outcome of the confusion assessment method for the ICU (CAM-ICU).[18] Patients received either haloperidol 2·5 mg or an equal volume (0·5 mL) of 0·9% saline placebo intravenously every 8 h, according to their group allocation. The first dose was given at either 8 am, 4 pm, or midnight, depending on the time of randomisation. The dosing regimen for this trial was based on existing clinical practice for management of delirium in critically ill patients by UK consultant intensivists, as established by the UK Intensive Care Foundation in 2008.[19] Study drug was discontinued in all patients on ICU discharge, when the patient was delirium-free for two consecutive days, or after a maximum of 14 days treatment, whichever came first. Study drug was not tapered in view of the short course of treatment and because patients were often discharged once they were free of delirium. Study drug was restarted if the patient was subsequently assessed positive for delirium by CAM-ICU within the 14 day study period.

Patients were maintained using fentanyl and propofol sedative infusions titrated to a Richmond agitation sedation scale (RASS) target of 0 to –1,[20] unless the consultant intensivist responsible for clinical management decided a deeper level of sedation was needed on a given day. RASS was assessed every 4 h. We did not use a formal pain score—analgesics were titrated according to the bedside nurse's judgment of the patient's level of comfort and pain. When a patient was oversedated—ie, one or more points deeper than target RASS after sedative infusions were stopped for more than 24 h—the dose of study drug was halved. When oversedation persisted for an additional 24 h, the study drug was stopped. Weaning from ventilation was according to a standard protocol and included spontaneous breathing trials (appendix). All patients were actively mobilised by the critical care physiotherapy team from admission using a step-wise programme according to daily clinical status, from passively moving the patient's limbs to walking with assistance. ICU patients with RASS scores of –2 and upward were routinely sat out of bed unless there was a contraindication.

If patients developed acute agitation (RASS +2 and above) while on study drug, they were assessed for reversible causes, which were treated. Identification and management of reversible causes of agitation were left to the bedside nurse and doctor responsible for the patient's clinical care and not recorded in trial data. If the patient's agitation did not resolve, the patient was given up to 10 mg of intravenous haloperidol in a 24 h period, in separate doses of 2·5–5·0 mg. The frequency and dose of any other antipsychotics given was also recorded.

All study patients had continuous electrocardiogram (ECG) monitoring plus a daily 12-lead ECG. If the QTc increased to more than 500 ms, study drug administration was temporarily withheld while any reversible causes, including hypokalaemia or hypomagnesaemia, were corrected. Once the QTc was less than 500 ms, study drug was restarted at half dose. If serum potassium and magnesium were normal or the study drug was already at half dose, the drug was stopped.

Patients were monitored for extrapyramidal symptoms daily using a modified Simpson-Angus scale.[21] If a patient developed extrapyramidal symptoms the study drug dose was halved. If the symptoms continued after 24 h despite dose reduction the study drug was stopped. Adverse events were assessed for possible relation to study drug for up to 30 days after enrolment.

Demographic characteristics were recorded at the time of enrolment. Data were recorded daily while the patient remained in ICU up to a maximum of 28 days.

	Haloperidol (n=71)	Placebo (n=70)
Age at randomisation (years)	67·9 (16·5)	68·7 (14·9)
Men	37 (52%)	45 (64%)
Time from ICU admission to randomisation (days)	0·9 (0·91)	0·88 (0·81)
Main diagnosis at ICU admission*		
Sepsis or ARDS	25 (35%)	27 (39%)
Pneumonia	20 (28%)	20 (29%)
Acute coronary syndrome or cardiac failure	5 (7%)	6 (9%)
Renal or hepatic failure	3 (4%)	3 (4%)
Haemorrhage	6 (8%)	4 (6%)
COPD	1 (1%)	2 (3%)
Drug overdose	2 (3%)	0
Other	10 (14%)	8 (11%)
Medical patient	42 (59%)	49 (70%)
Surgical patient	29 (41%)	21 (30%)
APACHE II score (points)	19·8 (6·2)	19·7 (6·9)

Data are mean (SD) or n (%). ICU=intensive-care unit. ARDS=acute respiratory distress syndrome. COPD=chronic obstructive pulmonary disease. APACHE=acute physiology and chronic health evaluation. *One patient in the haloperidol group had two main diagnoses.

Table 1: **Baseline characteristics**

	Haloperidol (n=71)	Placebo (n=70)
2 days CAM-ICU negative	20 (28%)	26 (37%)
Discharge from ICU	17 (24%)	12 (17%)
Oversedation	8 (11%)	5 (7%)
QTc 500 ms or over	7 (10%)	4 (6%)
Died	5 (7%)	4 (6%)
Discontinuation of active treatment	3 (4%)	7 (10%)
14 days after randomisation	3 (4%)	6 (9%)
Extrapyramidal symptoms	0	1 (1%)
Other	8 (11%)	5 (7%)

Data are number (%). CAM-ICU=confusion assessment method for the intensive-care unit.

Table 2: **Reasons for study drug termination**

See Online for appendix

	Haloperidol (n=71)	Placebo (n=70)	Difference (95% CI)* or RR (95% CI)*	p value
Alive, delirium-free, and coma-free days in first 14 days	5 (0–10)	6 (0–11)	−0·48 (−2·08 to 1·21)	0·53
Days in delirium in first 14 days†	5 (2–8)	5 (1–8)	0·01 (−1·31 to 1·33)	0·99
Days in coma in first 14 days†	0 (0–2)	0·5 (0–2)	0·00 (−0·68 to 0·67)	0·99
Alive, delirium–free, and coma-free days in first 28 days	19 (0–24)	19·5 (0–25)	−0·26 (−3·72 to 3·46)	0·57
Days in delirium in first 28 days†	5 (2–10)	5 (1–9)	−0·38 (−2·37 to 1·62)	0·71
Days in coma in first 28 days†	0 (0–2)	1 (0–2)	−0·05 (−0·82 to 0·72)	0·90
Ventilator-free days in first 28 days	21 (0–25)	17 (0–25)	0·25 (−3·26 to 4·16)	0·88
Mortality at 28 days	20 (28·2%)	19 (27·1%)	RR 1·04 (0·61 to 1·77)	..
Length of critical care stay (days)‡	9·5 (5–14)	9 (5–18)	−1·45 (−5·42 to 2·52)	0·47
Length of hospital stay (days)§	18·5 (12–31)	26 (15–40)	−5·13 (−21·75 to 11·48)	0·54

Data are number (%), median (IQR), unless otherwise specified. RR=risk ratio. *CI bootstrapped. †Including patients who died within study period. ‡Excluding patients who died in ICU: n=52 for haloperidol, n=51 for placebo. §Excluding patients who died in hospital: n=42 for haloperidol, n=47 for placebo.

Table 3: **Outcomes**

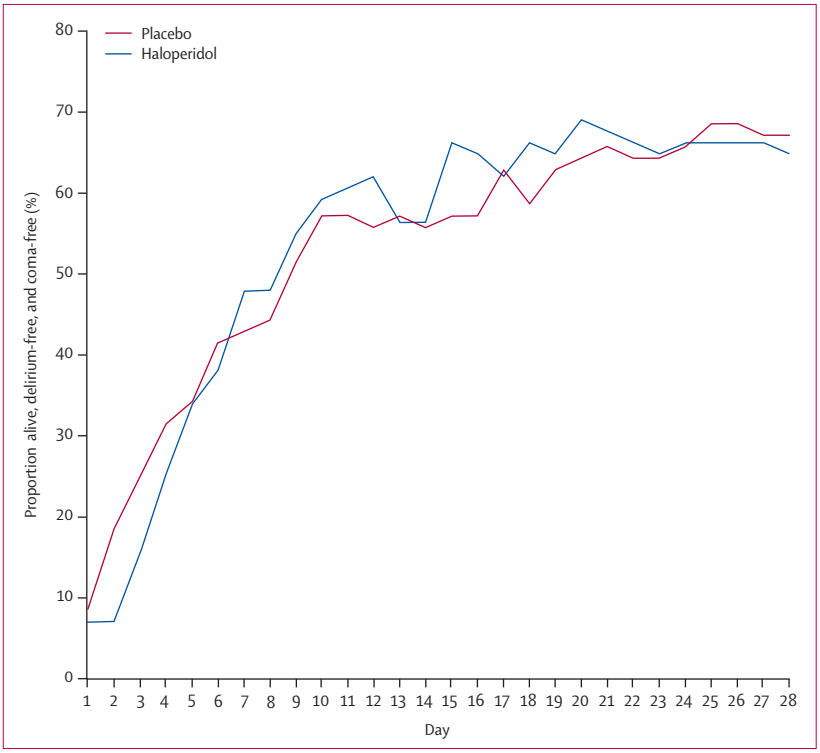

Figure 2: **Proportion of study patients with resolution of delirium over time**

The primary outcome was delirium-free and coma-free days, defined as the number of days in the first 14 days after randomisation during which the patient was alive without delirium and not in coma from any cause. Patients who died within the 14 day study period were recorded as having 0 days free of delirium and coma. This outcome measure best identifies improvement in the duration of normal cognitive status—ie, when the patient is alert and devoid of delirium.

Secondary outcomes were delirium-free and coma-free days to day 28, ventilator-free days from randomisation to day 28, mortality at 28 days, length of critical care and hospital stay, and safety with regard to prolonged QTc, extrapyramidal effects, and serious adverse events attributed to study drug. We defined ventilator-free days as the number of calendar days after a patient started unassisted breathing, for patients who survived at least 48 consecutive hours after the start of unassisted breathing.[22] Patients who died within 28 days of randomisation were counted as having no delirium-free and coma-free days or ventilator-free days.

Patients were defined as delirious if they were assessed with a RASS of –2 to +4, and screened positive for delirium by the bedside nurse using the CAM-ICU. Patients with a RASS score of –3 to –5 were classified as in a coma, irrespective of whether the state was induced by disease or sedation. Delirium was assessed using the CAM-ICU twice during each 12 h shift with a minimum of 4 h between the two assessment points. All assessments in a 24 h period needed to be negative for a patient to be delirium-free and coma-free. If any assessment was CAM-ICU positive in a midnight to midnight 24 h period, that day was recorded as "with delirium".

The study prespecified confounders were age, sex, and acute physiology and chronic health evaluation (APACHE) score.

Statistical analysis

Because the primary outcome has a non-normal distribution, we planned to use a non-parametric test for analysis. The power-efficiency of the Wilcoxon rank sum test is expected to be about 95% compared with a *t* test, and therefore the sample size needed for a Wilcoxon test would be 1·053 times as many as needed for a *t* test. To achieve a statistically significant result ($p<0·05$) with 80% power and a true treatment difference of 2 days (SD 0·5), 64 participants were needed per group. After increasing the number of recruits by 1·053 times and allowing for 5% loss to follow-up, the target sample size was 71 per group (142 total).

Analyses were done according to the intention-to-treat principle, all randomised participants were included, and were analysed in their randomised groups irrespective of treatment actually received. We compared dichotomous outcomes using risk ratios and 95% CIs. For the primary outcome and other outcomes expected to have substantially non-normal distributions, non-parametric tests comparing ranking of individual outcomes were used to calculate p values. To inform the size of difference and uncertainty we calculated the difference in means between the groups, and used bootstrapping to estimate 95% CIs. For other continuous outcomes, we used *t* tests and standard methods of calculating CIs. We checked normality of data using Shapiro-Wilk tests and Q-Q plots in SPSS. We used SAS (version 9.3) and SPSS (version 21) for analyses. This trial is registered with the International

Standard Randomised Controlled Trial Registry, number ISRCTN83567338.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. VJP, SG, and DFM had access to the raw data. The corresponding author (VJP) had full access to all data and final responsibility for the decision to submit for publication.

Results

Between Nov 9, 2010, and Sept 21, 2012, 677 patients were screened and 142 patients were enrolled; 71 patients were allocated to placebo and 71 to haloperidol (figure 1). One patient in the placebo group was withdrawn after failure to obtain consent to continue or use collected data, this patient's data were not included in the final analysis.

The two groups were much the same at baseline with regard to demographics, severity of illness, and ICU admission diagnoses (table 1). The mean number of doses of study drug per patient was 15·8 (SD 10·8) in the haloperidol group and 16·8 (11·2) in the placebo group. The reason study drug was discontinued in most patients was either because they screened negative for delirium on 2 consecutive days or were discharged from the ICU (table 2).

During the 14 day period from randomisation, patients in the haloperidol group spent about the same number of days alive without delirium and without coma as did patients in the placebo group (median 5 days [IQR 0–10] in the haloperidol group *vs* 6 days in the placebo group [0–11]; p=0·53; table 3). The number of days assessed as spent in delirium (as opposed to coma or normal) did not differ between the two groups (median 5 days [IQR 2–8] in the haloperidol group *vs* 5 days [1–8] in the placebo group; p=0·99). Figure 2 shows the daily rate of recovery from delirium and coma in both groups as the proportion of study patients alive, delirium-free, and coma-free. Ten patients restarted study drug because of new delirium within 14 days, seven in the haloperidol group and three in the placebo group. We identified no differences in secondary outcomes, including ventilator-free days, length of critical care stay, length of hospital stay, and mortality at 28 days (table 3).

In addition to the study drug, 18 patients in the placebo group and eight patients in the haloperidol group received additional open-label antipsychotic medication, most often haloperidol. Most patients received one or two doses of antipsychotic treatment. The risk of needing additional antipsychotic treatment was significantly lower in patients receiving haloperidol than in those in the placebo group (table 4). Patients in the placebo group received haloperidol for an average of 0·41 days (SD 1·0). Although there was no statistical difference between use of individual sedative or opioid drugs between groups, our results suggest that haloperidol might reduce the need for sedatives (table 5).

	Haloperidol (n=71)	Placebo (n=70)	Difference (95% CI) or RR (95% CI)	p value
Any antipsychotic*	8 (11%)	18 (26%)	RR 0·44 (0·20 to 0·94)	..
Open-label haloperidol				
Patients treated	6 (8%)	15 (21%)	RR 0·39 (0·16 to 0·96)	..
Number of days	0·17 (0·59)	0·41 (1·00)	Difference −0·25 (−0·52 to 0·03)	0·08
Total dose (mg)	1·0 (4·05)	1·71 (4·41)	Difference −0·71 (−2·12 to 0·70)	0·32

Data are n (%) or mean (SD) unless otherwise specified. RR=risk ratio. *In the haloperidol group, one patient received olanzapine and one patient received additional haloperidol and olanzapine. In the placebo group, two patients received haloperidol, olanzapine, and quetiapine, and one patient received haloperidol and olanzapine.

Table 4: **Use of other antipsychotics**

	Haloperidol (n=71)	Placebo (n=70)	Difference (95% CI*)	p value
Fentanyl				
Patients treated	62 (87%)	58 (83%)	..	
Total dose (mg)	8·62 (10·93)	14·24 (22·29)	−5·62 (−11·46 to 0·21)	0·06
Number of days	4·48 (3·40–5·56)	5·50 (4·11–6·89)	−1·02 (−2·76 to 0·72)	0·25
Propofol				
Patients treated	57 (80%)	63 (90%)	..	
Total dose (mg)	5308 (7663)	8170 (10 343)	−2862 (−5890 to 166)	0·06
Number of days	3·89 (4·35)	5·19 (4·38)	−1·30 (−2·75 to 0·16)	0·08
Clonidine				
Patients treated	5 (7%)	2 (3%)	..	
Total dose (mg)	0·71 (4·69)	0·18 (1·12)	0·53 (−0·61 to 1·67)	0·36
Number of days	0·20 (0·82)	0·14 (0·86)	0·05 (−0·23 to 0·33)	0·70
Midazolam				
Patients treated	15 (21%)	16 (23%)	..	
Total dose (mg)	8·37 (28·92)	48·74 (195·02)	−40·38 (−86·6 to 5·89)	0·09
Number of days	0·35 (0·81)	0·76 (2·16)	−0·41 (−0·95 to 0·14)	0·14
Morphine				
Patients treated	13 (18%)	16 (23%)	..	
Total dose (mg)	12·57 (52·65)	25·94 (77·49)	−13·37 (−35·40 to 8·66)	0·23
Number of days	0·56 (1·59)	0·50 (1·10)	0·06 (−0·39 to 0·52)	0·78

Data are n (%) or mean (SD) unless otherwise specified. *CI bootstrapped.

Table 5: **Use of sedatives and analgesics**

A secondary data analysis showed that a lower proportion of patients had a RASS of +2 or more in the haloperidol group than in the placebo group (median 13% [IQR 8·75–17·00] *vs* 20% [17·50– 26·75]; p=0·0075; figure 3).

The most common adverse event was oversedation (11 [15%] in haloperidol group *vs* six [9%] in placebo group; table 6). No serious adverse events were attributable to the study drug (table 6). QTc prolongation of 500 ms or more occurred in seven patients receiving haloperidol compared with six patients in the placebo group. Two patients in the placebo group had halving of the study drug because of QT prolongation, which responded to correction of plasma electrolytes. Eleven of the patients had the study drug stopped, of whom two patients in the haloperidol group

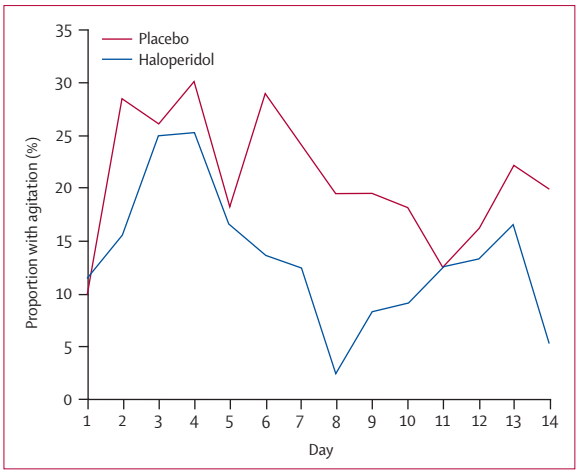

Figure 3: **Study patients with agitation in first 14 days**

	Haloperidol	Placebo
All		
Oversedation	11 (15%)	6 (9%)
Decreased consciousness*	2 (3%)	1 (1%)
Self-extubation	1 (1%)	2 (3%)
QTc prolongation >500 ms	7 (10%)	6 (9%)
Sinus tachycardia	0	1 (1%)
Atrial fibrillation	7 (10%)	3 (4%)
Supraventricular tachycardia	4 (6%)	1 (1%)
Ventricular ectopics	0	1 (1%)
Bradycardia	2 (3%)	0
Non-specific ECG changes	0	2 (3%)
Hypotension	3 (4%)	2 (3%)
Desaturation	1 (1%)	1 (1%)
Akathisia	1 (1%)	2 (3%)
Excessive salivation	2 (3%)	0
Muscle stiffness	1 (1%)	1 (3%)
Torticollis	0	1 (3%)
Blurred vision	1 (3%)	0
Serious		
Apnoea post treatment for agitation	0	1 (3%)
Fast atrial fibrillation with hypotension	1 (3%)	0
Readmission to ICU with sepsis	1 (3%)	1 (1%)
Failed extubation	1 (3%)	3 (4%)

Data are n (%). 13 participants had more than one event. *Not sedation-related.

Table 6: **Adverse events**

had been already on half dose study drug when QTc over 500 ms, one for over sedation and one for excessive salivation. None of these patients had ventricular arrhythmias and specifically no patient had an episode of torsades de pointes. Extrapyramidal symptoms sufficient to stop the study drug occurred in only one patient, who was receiving placebo. Study drug was stopped in eight patients in the haloperidol group and five patients in the placebo group because of oversedation in patients who were no longer on sedative or analgesic infusions (table 2). Three patients were thought to have akathisia, only one of whom was on haloperidol, the study drug was halved, and in one patient who was not on haloperidol, the drug was already at half dose so the drug was stopped.

Discussion

In this study, early treatment with haloperidol did not modify the prevalence or duration of delirium or coma in critically ill patients needing mechanical ventilation. The average duration of delirium in these patients was about 5 days in both groups. Furthermore, haloperidol did not have an effect on any secondary clinical outcomes.

Only four placebo-controlled efficacy trials of antipsychotics in critical care patients have been reported, all with limitations either in type or number of patients or study design (panel).[23–31] Studies in critically ill patients using haloperidol are limited in quality, such that the recent pain, agitation, and delirium clinical practice guidelines from the American College of Critical Care Medicine concluded that no recommendation could be made regarding the use of haloperidol to prevent or treat delirium in adult ICU patients.[30] One trial[28] in 457 post-operative, mainly elective, patients admitted to ICUs in Beijing did show a reduction in the incidence of delirium using prophylactic, low dose haloperidol (0·5 mg bolus injection followed by an infusion of 0·1 mg/h for 12 h) compared with placebo. The study population was not critically ill, with a mean APACHE score of less than nine and a median ICU stay of less than 24 h. Only 35 patients (15·3%) in the haloperidol group and 53 patients (23·2%) in the placebo group developed delirium. A smaller pilot study[29] done in the USA did not show a reduction in ICU delirium using enteral haloperidol or ziprasidone, but was designed to assess feasibility, not powered for clinical outcomes. A before-and-after study seemed to show that low dose haloperidol prophylaxis in higher risk critically ill patients might have beneficial effects, although this study design had limitations.[14]

Although our study was not powered to show a difference between the use of individual psychotropic or opioid drugs between groups, our results suggest that haloperidol might reduce the need for sedatives. Propofol is mainly metabolised by cytochrome P450, isoform CYP2B6, and it has been shown in vitro to inhibit CYP3A4, an isoform involved in the biotransformation of haloperidol in human beings.[32,33] Data suggest the degree of inhibition of CYP3A4 by propofol would be unlikely to have any pronounced clinical significance.[34] This was not a mechanistic study and the pharmacokinetic and genetic factors affecting individual patient CYP activity and different drugs are complex. Since there was no difference in delirium or coma with the use of haloperidol it is unlikely any pharmacokinetic interaction had any significant effect on the primary outcome. The decreased exposure to sedative drugs in the haloperidol group did not translate into more delirium-free, coma-free days, which is consistent with the

results of a study[35] comparing biological and drug treatment characteristics in 99 ICU patients with coma or delirium, or both, which showed that unlike coma, delirium was unrelated to sedative exposure. Agitation remains the most common motivation for use of haloperidol in critically ill patients and a lower proportion of patients had a RASS of +2 or more in the group who received haloperidol compared with those who received placebo. Thus, haloperidol is a useful agent for management of agitation despite having no effect on delirium.

The strengths of this study include the study design as a randomised, double-blind, placebo-controlled trial. Patients were started on the study drug early irrespective of whether they had screened positive for delirium or were in coma. The power calculations on which this study is based support that the number of patients included would show a difference of alive, delirium-free, coma-free days if any existed. As a randomised controlled trial any confounding variables would be expected to be present equally between the two groups, and there was no indication of imbalance in baseline variables measured. The low median number of days patients spent in coma in the first 14 days (0 days [IQR 0–2] in the haloperidol group *vs* 0·5 days [0–2] in the placebo group) suggests that patients were managed in keeping with a RASS range of 0 to –2, ie, not deep sedation.[36]

The study has several limitations. This was a single site study, although the population of patients was broadly representative of the general ICU population in the UK and internationally. As with most critical care research, the patients' admission diagnoses were wide ranging and the number of surgical patients and those with an admission diagnosis of sepsis were much the same in both groups. There might have been an imbalance of risk factors for which data were not collected; however, we would not expect such an imbalance in a randomised trial. It might be that a subset of critically ill patients (eg, those with established delirium) would benefit from routine haloperidol, although in view of the results of this study the benefit would probably be small, and a much larger study would be needed to show it.

Defining normal cognitive function as the absence of delirium and coma in a patient is an inevitable constraint because it is not possible to be confident in delineating the cause of coma as disorder or drugs in many ICU patients. Hence we used a clinical diagnosis based on the absence of symptoms, using a valid instrument but without attempting to claim causality, then collected observations as to the persistence or not of symptoms. An intervention to reduce days with delirium could achieve its goal not by increasing days without delirium, but by increasing days with coma. We used the combination of delirium-free and coma-free to ensure that a reduction in delirium was indicative of a patient's brain recovering towards a normal state, rather than moving into coma.

Patients who died within 14 days were assessed with zero delirium-free, coma-free days to manage the possible conflicting effects of haloperidol on delirium and survival in the same way that days alive and free from mechanical ventilation are used as an outcome measure in treatments for adult respiratory distress syndrome.[22] If haloperidol was associated with increased mortality in the first 14 days, then haloperidol might be reported to improve delirium, even though this effect might be attributable to patients dying earlier, which is clearly not beneficial. The number of days in delirium and days in coma in all patients are presented in table 3, which when considered with the secondary outcome of mortality, show the groups do not differ. Thus in patients who died of an unrelated cause, haloperidol did not modulate delirium.

Although we cannot confidently exclude an effect with a much higher dose of haloperidol, PET scan studies show that doses of 2–5 mg per day, giving plasma concentrations of 1–2 ng/mL, induce 60–80% dopamine D2 receptor occupancy; 70% is deemed adequate for typical neuroleptic response.[37] Furthermore Medsafe, the New Zealand medicines safety authority, have reviewed available data and recommend that doses greater than 10 mg per day are unlikely to provide further efficacy, but might lead to increased adverse effects.[38]

The dose of haloperidol might be considered large outside of the critical care setting. The British Geriatric Society guidelines recommend 0·5 mg orally up to every 2 h. In patients taking oral haloperidol 2 mg daily, mean plasma haloperidol concentrations were about twice as

Panel: Research in context

Systematic review

We searched PubMed with the key words "intensive care", "critical care", "delirium", and "antipsychotics", for studies reported in English up to April 18, 2013. We included only studies in adult patients. There are three relevant Cochrane reviews.[23–25] They concluded that although low dose haloperidol might be effective in postoperative patients, there was a scarcity of robust information on delirium prevention and that in terminally ill patients there was little evidence for the role of drug therapy in management of delirium. Four placebo-controlled randomised trials[26–29] have been done in intensive-care unit (ICU) patients, with variable results, from small effects to no benefit. However, two of these trials were small. There are some reports of harm with the use of antipsychotics in elderly patients.

Clinical practice guidelines[30] for the sustained use of sedatives and analgesics in the critically ill adult were reported in January, 2013, based on a review of evidence identified from a systematic review, guided by key words provided by four subcommittees of experts. With regard to delirium the subcommittee identified no double-blind, randomised, placebo-controlled trials of adequate power to establish the efficacy or safety of any antipsychotic agent in the management of delirium in ICU patients. They also concluded that robust data for haloperidol in non-ICU patients, which could potentially be applied to the ICU setting, are absent.

Interpretation

As far as we are aware, our study is the first double-blind, randomised, controlled efficacy trial designed and powered to establish whether haloperidol will modify delirium in critically ill patients. We identified no difference between the haloperidol and placebo groups. This finding supports UK National Institution of Clinical Excellence guidelines,[31] based on expert opinion, that antipsychotics should only be used when non-pharmacological methods have not worked and a patient is distressed or a danger to themselves or others.

high in elderly patients compared with adult patients with schizophrenia.[39] However, a US survey of 250 critical care pharmacists from eight states confirmed that more than 50% use a scheduled daily dose of 5–10 mg intravenously, in keeping with this study dose which was informed by the UK Intensive Care Foundation survey of current practice.[7,40]

Our group of patients had a high prevalence of coma (deep sedation) or delirium in the first 48 h. Our previous data suggested that at least 65% would have delirium.[8] However, since we included patients who were assessed as RASS –3 in the present study, we expected the prevalence to be higher. This expectation was in keeping with data from the Australian and New Zealand Intensive Care Society (ANZICS), which showed that more than 75% of patients had a RASS of –3 or worse early in the course of ICU stay.[36] The low numbers of patients assessed as free of delirium and coma could also be due to the frequency and timing of RASS and CAM-ICU assessments; study patients were assessed four times daily and only needed to have one assessment of RASS –3 or less, or screen positive once for delirium for that day, to count as not delirium-free or coma-free. Additionally, according to the ANZICS data, patients were more likely to be assessed as not being delirium or coma free when an assessment was done soon after the patient was sedated and ventilated.

The use of open label antipsychotics when clinically indicated meant that some placebo patients received antipsychotics and therefore were not truly receiving placebo alone. However, the amounts used were minimal and there was no difference between the overall doses of open label haloperidol used (mean 1·0 mg [SD 4·05] in haloperidol group *vs* 1·71 mg [4·41] in the placebo group). Currently, the belief in the efficacy of haloperidol in delirium is such that it was not possible to obtain ethical approval to undertake a placebo-controlled trial without allowing the option of rescue haloperidol.

Abruptly stopping haloperidol after a patient screened negative for 2 days might have resulted in the loss of a sustained preventive effect. Since intravenous haloperidol is not generally used outside of critical care and being delirium free would suggest clinical improvement such that discharge from critical care would be anticipated, we believed that stopping the study drug after 2 days would be most practically and clinically relevant. In fact, ten patients needed to restart the study drug for new delirium, seven patients receiving haloperidol and three receiving placebo. The assumption that once a patient had been discharged from the ICU, they were free of delirium is also a limitation of this study. We used the CAM-ICU as a relevant instrument to detect delirium in this ICU study population. It has been endorsed by the American College of Critical Care Medicine as a valid and reliable non-verbal instrument and this notion has been confirmed by a meta-analysis.[30,41] However, the CAM-ICU has not been shown to be a valid delirium-screening instrument outside of the critical care environment.[42] Episodes of delirium would be expected to negatively affect clinical progress of patients once discharged from the ICU, potentially leading to longer hospital stays.[43] However, since length of hospital stay did not differ between the two groups, it is unlikely that undocumented episodes of delirium after ICU discharge, within the 14 day study period, would change the result of the primary outcome.

Despite a limited evidence base, increasing numbers of patients are being exposed to haloperidol for the management of delirium. Our results suggest a commonly used haloperidol dose regimen does not decrease delirium in an unselected population of critically ill patients requiring mechanical ventilation, when commenced early during ICU stay. Identification of a pharmacological intervention to prevent or reduce delirium and improve adverse outcomes, including in the ICU setting, remains a high priority within delirium research.[28]

Contributors

VJP, EWE, GDP, and DFM were responsible for conception and contributed to design, analysis, and interpretation of data, drafting of the manuscript, and obtaining funding. SG and AS contributed to design, statistical analysis, and interpretation of data. TA and XBZ contributed to acquisition of data, drafting of the manuscript, and provided administrative support. JJ contributed to study design and critical revision of the manuscript.

Conflicts of interest

VJP has received honoraria from Orion. EWE has received honoraria from Hospira, Orion, and Abbott. DM has received honoraria from GlaxoSmithKline, Orion, and AstraZeneca. The other authors declare that they have no conflicts of interest. DFM and GDP are codirectors of research for the UK Intensive Care Foundation.

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References

1 Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; **291:** 1753–62.

2 Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009; **180:** 1092–97.

3 Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; **38:** 1513–20.

4 Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007; **33:** 66–73.

5 Peterson J, Pun B, Dittus R, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 2006; **54:** 479–84.

6 Pisani M, Murphy T, Ness P, Araujo K, Inouye S. Characteristics associated with delirium in older patients in a medical intensive care unit. *Arch Intern Med* 2007; **167:** 1629–34.

7 Salluh JI, Soares M, Teles JM, et al. Delirium epidemiology in critical care (DECCA): an international study. *Crit Care* 2010; **14:** R210.

8 Page VJ, Navarange S, Gama S, McAuley DF. Routine delirium monitoring in a UK critical care unit. *Crit Care* 2009; **13:** R16.

9 Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin* 2008; **24:** 789–856.

10 Etezadi F, Najafi A, Yarandi KK, Moharari RS, Khajavi MR. ICU sedation with haloperidol-propofol infusion versus midazolam-propofol infusion after coronary artery bypass graft surgery: a prospective, double-blind randomized study. *Ann Card Anaesth* 2012; **15:** 185–89.

11 Milbrandt EB, Kersten A, Kong L, et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. *Crit Care Med* 2005; **33:** 226–29.

12 Moots R, Al-Saffar Z, Hutchinson D, et al. Old drug, new tricks: haloperidol inhibits secretion of proinflammatory cytokines. *Ann Rheum Dis* 1999; **58:** 585–87.

13 Devlin J, Al-Qadheeb NS, Skrobik Y. Pharmacologic prevention and treatment of delirium in critically ill and non-critically ill hospitalized patients: a review of data from prospective randomized studies. *Best Pract Res Clin Anaesthesiol* 2012; **26:** 289–309.

14 van den Boogaard M, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. *Crit Care* 2013; **17:** R9.

15 Patel RP, Gambrell M, Speroff T, et al. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. *Crit Care Med* 2009; **37:** 825–32.

16 Wang P, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; **353:** 2335–41.

17 Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ* 2012; **344:** e977.

18 Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; **29:** 1370–79.

19 Mac Sweeney R, Barber V, Page V, et al. A national survey of the management of delirium in UK Intensive Care Units. *QJM* 2010; **103:** 243–51.

20 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166:** 1338–44.

21 Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970; **212** (suppl)**:** 11–19.

22 Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; **30:** 1772–77.

23 Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M. Drug therapy for delirium in terminally ill adult patients. *Cochrane Database Syst Rev* 2012; **11:** CD004770.

24 Lonergan E, Britton AM, Luxenberg J. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007; **2:** CD005594.

25 Siddiqi N, Holt R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev* 2007; **2:** CD005563.

26 Prankanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care* 2007; **35:** 714–19.

27 Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010; **38:** 419–27.

28 Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. *Crit Care Med* 2012; **40:** 731–39.

29 Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; **38:** 428–37.

30 Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41:** 263–306.

31 Young J, Murthy L, Westby M, Akunne A, O'Mahony R. Diagnosis, prevention, and management of delirium: summary of NICE guidance. Guideline Development Group. *BMJ* 2010; **341:** c3704.

32 Yang L, Yu W, Cao Y, Gong B, Chang Q, Yang G. Potential inhibition of cytochrome P4503A4 by propofol in human primary hepatocytes. *World J Gastroenterol* 2003; **9:** 1959–62.

33 Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. *Clin Pharmacokinet* 1999; **37:** 435–56.

34 McKillop M, Wild M, Butters C, Simcock C. Effects of propofol on human hepatic microsomal cytochrome P450 activities. *Xenobiotica* 1998; **28:** 845–53.

35 Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1 and ABCG2 genetic polymorphisms and inflammatory factors. *Crit Care Med* 2013; **41:** 999–1008.

36 Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012; **186:** 724–31.

37 Kapur S, Zipursky R, Roy P, et al. The relationship between D2 occupancy and plasma levels on low dose oral haloperidol: a PET study. *Psychopharmacology* 1997; **131:** 148–52.

38 Medsafe. Haloperidol—dose recommendations. http://www.medsafe.govt.nz/profs/PUArticles/Dec2012Haloperidol.htm (accessed July 1, 2013).

39 Chang WH, Jann MW, Chiang TS, Lin HN, Hu WH, Chien CP. Plasma haloperidol and reduced haloperidol concentrations in a geriatric population. *Neuropsychobiology* 1996; **33:** 12–16.

40 Devlin JW, Bhat S, Roberts RJ, Skrobik Y. Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states. *Ann Pharmacother* 2011; **45:** 1217–29.

41 Gusmao-Flores D, Figueira Salluh J, Chalhub R, Quarantini L. The confusion assessment method for the intensive care unit (CAM-ICU) and the intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: as systematic review and meta-analysis of clinical studies. *Crit Care* 2012; **16:** R115.

42 Neufeld KJ, Hayat MJ, Coughlin JM, et al. Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. *Psychosomatics* 2011; **52:** 133–40.

43 Zhang Z, Pan L, Ni H. Impact of delirium on clinical outcome in critically ill patients: a meta-analysis. *Gen Hosp Psychiatry* 2013; **35:** 105–11.